

THERAPEUTIC CARBAMATES

CROSS-REFERENCE TO RELATED APPLICATIONS:

This application is a continuation-in-part of U.S. Patent Application Serial
10 No. 09/456,170, filed December 7, 1999.

BACKGROUND OF THE INVENTION

A receptor is a biological structure with one or more binding domains that reversibly complexes with one or more ligands, where that complexation has
15 biological consequences. Receptors can exist entirely outside the cell (extracellular receptors), within the cell membrane (but presenting sections of the receptor to the extracellular milieu and cytosol), or entirely within the cell (intracellular receptors). They may also function independently of a cell (e.g., clot formation). Receptors within the cell membrane allow a cell to communicate with
20 the space outside of its boundaries (i.e., signaling) as well as to function in the transport of molecules and ions into and out of the cell.

A ligand is a binding partner for a specific receptor or family of receptors. A ligand may be the endogenous ligand for the receptor or alternatively may be a synthetic ligand for the receptor such as a drug, a drug candidate or a
25 pharmacological tool.

The super family of seven transmembrane proteins (7-TMs), also called G-protein coupled receptors (GPCRs), represents one of the most significant classes of membrane bound receptors that communicate changes that occur outside of the cell's boundaries to its interior, triggering a cellular response when appropriate.
30 The G-proteins, when activated, affect a wide range of downstream effector systems both positively and negatively (e.g., ion channels, protein kinase cascades, transcription, transmigration of adhesion proteins, and the like).

Muscarinic receptors are members of the G-protein coupled receptors that are composed of a family of five receptor sub-types (M_1 , M_2 , M_3 , M_4 and M_5) and are activated by the neurotransmitter acetylcholine. These receptors are widely distributed on multiple organs and tissues and are critical to the maintenance of

5 central and peripheral cholinergic neurotransmission. The regional distribution of these receptor subtypes in the brain and other organs has been documented (Bonner, T. I. et al., *Science* (Washington D.C.) 1987, 237, 527-532; Goyal, R. K., *J. Med.*, 1989, 321, 1022; Hulme, E.C., et al., *Annu. Rev. pharmacol. Toxicol.* 1990, 30, 633; and Eglen, R. M. and Hegde, S. S., *Drug News Perspect.* 1997, 10(8), 462-469).

10 For example, the smooth muscle is composed largely of M_2 and M_3 receptors, cardiac muscle is composed largely of M_2 receptors, and salivary glands are largely composed of M_3 receptors.

It has been established that the muscarinic receptors are involved in diseases such as chronic obstructive pulmonary disease, asthma, irritable bowel syndrome, 15 urinary incontinence, rhinitis, spastic colitis, chronic cystitis, cognitive disorders (e.g. Alzheimer's disease), senile dementia, glaucoma, schizophrenia, gastroesophageal reflux disease, cardiac arrhythmia, blurred vision, and hyper salivation syndromes (Fisher, A., *Invest. Drugs*, 1997, 6(10), 1395-1411; Martel, A. M., et al., *Drugs Future*, 1997, 22(2), 135-137; Graul, A. and Castaner, J., *Drugs Future*, 1996, 21(11), 1105-1108; and Graul, A., et al., *Drugs Future*, 1997, 22(7), 733-737).

A number of compounds having muscarinic receptor antagonistic activities are being used to treat these diseases. For example, oxybutynin is being used for the treatment of urinary urge incontinence and dicyclomine is being used for the 25 treatment of irritable bowel syndrome. However, these drugs have limited utility as they produce side effects such as dry mouth, blurred vision, and mydriasis.

There is currently a need for novel muscarinic receptor antagonists.

SUMMARY OF THE INVENTION

The invention is directed to carbamate derivatives that are muscarinic receptor antagonists and agonists and are useful in the treatment and prevention of diseases mediated by muscarinic receptors (e.g. chronic obstructive pulmonary disease, chronic bronchitis, irritable bowel syndrome, urinary incontinence, and the like).

Accordingly, the invention provides a compound of the invention which is a compound of Formula (I):

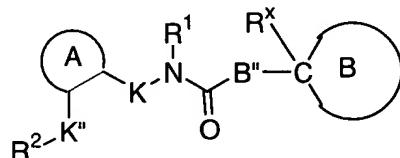
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L_1-X-L_2

wherein:

L_1 is a group of formula (a):

15



(a)

wherein:

20 A is an aryl or a heteroaryl ring;

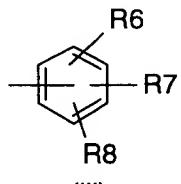
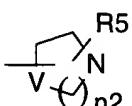
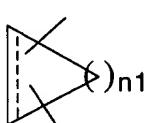
B'' is -O-;

R^x is alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, acyl, acylamino, aminoacyloxy, aryl, carboxyalkyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl,

25 heteroaralkyl, alkylsulfonyl, or alkylsulfinyl;

R¹ is hydrogen or alkyl;

R² is Het, or is selected from a group consisting of formula (i), (ii), and (iii):



wherein:

----- is an optional double bond;

n_1 is an integer of from 1 to 4;

n_2 is an integer of from 1 to 3;

5 V is $-\text{CH}-$, $-\text{O}-$, $-\text{S}(\text{O})\text{n}_3-$ (where n_3 is an integer of from 0 to 2), or $-\text{NR}^4-$

(wherein R⁴ is hydrogen, alkyl, substituted alkyl, aryl, or heteroaryl);

“Het” is a heteroaryl ring which optionally attaches (a) to a linker;

R^3 is hydrogen, alkyl, amino, substituted amino, -OR^a (where R^a is hydrogen, alkyl, or acyl), or a covalent bond attaching (a) to a linker;

10 R⁵ is hydrogen, alkyl, amino, substituted amino, -OR^b (where R^b is hydrogen or alkyl), aryl, aralkyl, heteroaralkyl, or a covalent bond attaching (a) to a linker;

R^6 , R^7 , and R^8 are, independently of each other, hydrogen, halo, hydroxy, alkoxy, haloalkoxy, carboxy, alkoxycarbonyl, alkyl optionally substituted with one, two or three substituents selected from halo, hydroxy, carboxy, alkoxycarbonyl,

15 alkylthio, alkylsulfonyl, amino, substituted amino, or a covalent bond attaching (a) to a linker;

K is a bond or an alkylene group;

K" is a bond, -C(O)-, -S(O)_{n4}- (where n₄ is an integer of from 0 to 2), or an alkylene group optionally substituted with a hydroxyl group; and

20 B is heterocycloamino or heteroaryl amino, which optionally attaches (a) to a linker;

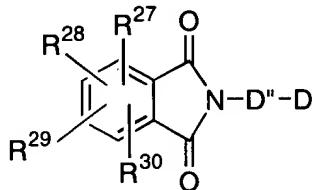
provided that at least one of the R^5 , R^6 , R^7 , R^8 , "Het", heterocycloamino or heteroaryl amino groups attaches (a) to a linker;

X is a linker; and

L₂ is an organic group comprising at least one (e.g. 1, 2, 3, or 4) primary, secondary or tertiary amines; or a pharmaceutically acceptable salt; or prodrug thereof.

5 Preferably, L₂ is a group selected from a group consisting of:

(i) a group of formula (b):



(b)

wherein:

Dⁿ is alkylene;

10 D is -NR³¹R³², -N⁺(R³³R³⁴R³⁵) or -OR³² where R³¹, R³³, and R³⁴ are, independently of each other, hydrogen, alkyl, or aralkyl; and R³² and R³⁵ represent a covalent bond attaching (b) to a linker;

15 R²⁷ is hydrogen, halo, nitro, cyano, hydroxy, alkoxy, carboxy, alkoxycarbonyl, acyl, thio, alkylthio, alkylsulfonyl, alkylsulfinyl, sulfonamido, alkylsulfonamido, carbamoyl, thiocarbamoyl, mono or dialkylcarbamoyl, amino, mono- or dialkylamino, aryl, aryloxy, arylthio, heteroaryl, heteraryloxy, heteroarylthio, heterocyclyl, heterocyclyloxy, aralkyl, heteroaralkyl, or alkyl optionally substituted with one, two or three substituents selected from halo, hydroxy, carboxy, alkoxycarbonyl, alkylthio, alkylsulfonyl, amino, or substituted amino;

20 R²⁸ is hydrogen, halo, nitro, cyano, hydroxy, alkoxy, carboxy, alkoxycarbonyl, acyl, thio, alkylthio, alkylsulfonyl, alkylsulfinyl, sulfonamido, alkylsulfonamido, carbamoyl, thiocarbamoyl, mono or dialkylcarbamoyl, amino, mono- or dialkylamino, or alkyl optionally substituted with one, two, or three

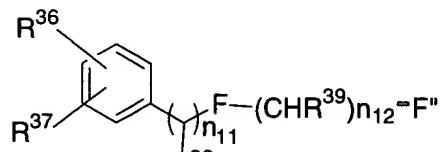
substituents selected from halo, hydroxy, carboxy, alkoxy carbonyl, alkylthio, alkylsulfonyl, amino, or substituted amino;

R^{29} and R^{30} are, independently of each other, hydrogen, alkyl, haloalkyl, halo, nitro, cyano, hydroxy, alkoxy, alkoxy carbonyl, acyl, thio, alkylthio, amino,

5 mono- or dialkylamino; or

one of R^{27} , R^{28} , R^{29} , or R^{30} together with the adjacent group forms a methylenedioxy or ethylenedioxy group;

(ii) a group of formula (c):



(c)

wherein:

10 n_{11} is an integer of from 1 to 7;

n_{12} is 0 to 7;

F is -NR⁴⁰-, -O-, -S-, or -CHR⁴¹- (wherein R⁴⁰ and R⁴¹ are, independently of each other, hydrogen, alkyl, or substituted alkyl);

F'' is a covalent bond, $-\text{OR}^{43}$, $-\text{NR}^{42}\text{R}^{43}$, or $-\text{N}^+\text{R}^{43}\text{R}^{44}\text{R}^{45}$ wherein R^{42} is

15 hydrogen or alkyl, R^{44} and R^{45} are alkyl, and R^{43} is hydrogen, alkyl, or a covalent bond attaching (c) to a linker;

R^{36} is hydrogen, alkyl, halo, nitro, cyano, hydroxy, alkoxy, carboxy, alkoxycarbonyl, acyl, thio, alkylthio, alkylsulfonyl, alkylsulfinyl, sulfonamido, alkylsulfonamido, carbamoyl, thiocarbamoyl, mono or dialkylcarbamoyl, amino,

20 mono- or dialkylamino, aryl, aryloxy, arylthio, heteroaryl, heteroaryloxy, heteroarylthio, heterocyclyl, heterocyclyloxy, aralkyl, heteroaralkyl, or alkyl optionally substituted with one, two or three substituents selected from halo,

hydroxy, carboxy, alkoxy carbonyl, alkylthio, alkylsulfonyl, amino, or substituted amino;

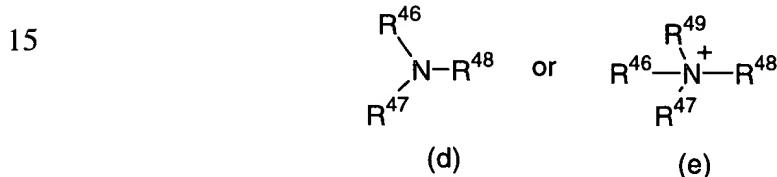
R^{37} is hydrogen, alkyl, halo, nitro, cyano, hydroxy, alkoxy, alkoxycarbonyl, acyl, thio, alkylthio, amino, mono- or dialkylamino, aryl, aryloxy, arylthio,

5 heteroaryl, heteraryloxy, heteroarylthio, heterocyclyl, heterocyclyoxy, aralkyl, heteroaralkyl, or alkyl optionally substituted with one, two or three substituents selected from halo, hydroxy, carboxy, alkoxy carbonyl, alkylthio, alkylsulfonyl, amino, or substituted amino; and

R^{38} is hydrogen, alkyl, halo, hydroxy, alkoxy, or a covalent bond attaching the ligand to a linker provided that at least one of R^{38} and R^{43} attaches (c) to a linker;

R³⁹ is hydrogen, alkyl, halo, hydroxy, alkoxy, or substituted alkyl; and

(iii) a group of formula (d) or (e):



wherein:

20 R⁴⁶ is alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, or heterocycle;

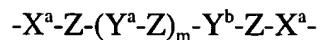
R^{47} is alkyl, substituted alkyl, aryl, acyl, heterocycle, or $-COOR^{50}$ where R^{50} is alkyl; or

R^{46} and R^{47} together with the nitrogen atom to which they are attached form 25 heterocycle, which heterocycle, in addition to optionally bearing the optional substituents defined hereinbelow for a heterocycle, can also optionally be substituted with one or more (e.g. 1, 2, 3, or 4) alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, or substituted alkynyl.

R⁴⁸ is a covalent bond that attaches the (d) to a linker; and

R⁴⁹ is alkyl;

Preferably X is a group of formula:



5 wherein

m is an integer of from 0 to 20;

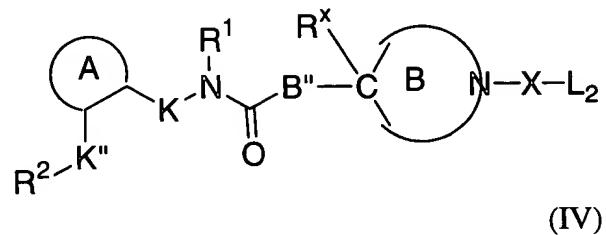
X^a at each separate occurrence is selected from the group consisting of -O-, -S-, -NR-, -C(O)-, -C(O)O-, -C(O)NR-, -C(S)-, -C(S)O-, -C(S)NR- or a covalent bond where R is as defined below;

10 Z at each separate occurrence is selected from the group consisting of alkylene, substituted alkylene, cycloalkylene, substituted cycloalkylene, alkenylene, substituted alkenylene, alkynylene, substituted alkynylene, cycloalkenylene, substituted cycloalkenylene, arylene, heteroarylene, heterocyclene, or a covalent bond;

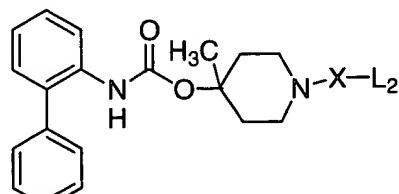
15 Y^a and Y^b at each separate occurrence are selected from the group consisting of -O-, -C(O)-, -OC(O)-, -C(O)O-, -NR-, -S(O)_n-, -C(O)NR'-, -NR' C(O)-, -NR' C(O)NR'-, -NR' C(S)NR'-, -C(=NR')-NR'-, -NR'-C(=NR')-, -OC(O)-NR'-, -NR'-C(O)-O-, -N=C(R")-NR'-, -NR'-C(R")=N-, -P(O)(OR')-O-, -O-P(O)(OR')-, -S(O)_nCR' R''-, -S(O)_n-NR'-, -NR'-S(O)_n-, -S-S-, and a covalent bond; where *n* is

20 0, 1 or 2; and R, R' and R'' at each separate occurrence are selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, cycloalkenyl, substituted cycloalkenyl, alkynyl, substituted alkynyl, aryl, heteroaryl and heterocyclic (preferably, at least one of X^a, Y^a, Y^b or Z is not a covalent bond).

The invention also provides a compound of the invention which is a compound of formula (IV):



wherein L₂ is an organic group comprising at least one (e.g. 1, 2, 3, or 4) primary, 5 secondary or tertiary amine; and wherein R², K'', A, K, R¹, R^X, and X have any of the values defined herein; or a pharmaceutically acceptable salt; or prodrug thereof. A preferred compound of the invention which is a compound of formula (IV) is a compound of formula (IVa):



(IVa)

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The invention also provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of the invention or a pharmaceutically acceptable salt or prodrug thereof.

The invention also provides synthetic intermediates disclosed herein, as well 15 as synthetic methods useful for preparing such intermediates, and synthetic methods useful for preparing compounds of the invention or salts thereof.

The invention also provides a method of treating diseases mediated by a muscarinic receptor in a mammal, comprising administering to said mammal a

therapeutically effective amount of a compound of the invention or a pharmaceutically acceptable salt or prodrug thereof.

The invention also provides a compound of the invention or a pharmaceutically acceptable salt or prodrug thereof for use in medical therapy, as well as the use of a compound of Formula (I) or a pharmaceutically acceptable salt or prodrug thereof in the preparation of a medicament for the treatment of a disease mediated by a muscarinic receptor in a mammal.

Applicant has discovered that hindered carbamate compounds of the present invention i.e., compounds having a tetra-substituted atom bonded to the carbamate oxygen, are metabolically more stable than compounds lacking such a tetra-substituted atom. Accordingly, compounds of the present invention have longer metabolic half-lives and/or longer duration of action *in vivo*, which can reduce the dose required for administration or can reduce the likelihood of the generation of unwanted metabolites.

15

DETAILED DESCRIPTION OF THE INVENTION

The following terms have the following meanings unless otherwise indicated. Any undefined terms have their art recognized meanings.

The term "alkyl" refers to a monoradical branched or unbranched saturated hydrocarbon chain preferably having from 1 to 40 carbon atoms, more preferably 1 to 10 carbon atoms, and even more preferably 1 to 6 carbon atoms. This term is exemplified by groups such as methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *n*-hexyl, *n*-decyl, tetradecyl, and the like.

The term "substituted alkyl" refers to an alkyl group as defined above wherein one or more carbon atoms in the alkyl chain have been optionally replaced with a heteroatom such as -O-, -S(O)_n- (where n is 0 to 2), -NR- (where R is hydrogen or alkyl) and having from 1 to 5 substituents selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, aminoacyl,

aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocycloxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocycloxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-
5 aryl, -SO-heteroaryl, -SO₂-alkyl, -SO₂-aryl, -SO₂-heteroaryl, and -NR^aR^b, wherein R^a and R^b may be the same or different and are chosen from hydrogen, optionally substituted alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, heteroaryl and heterocyclic. This term is exemplified by groups such as hydroxymethyl, hydroxyethyl, hydroxypropyl, 2-aminoethyl, 3-aminopropyl, 2-
10 methylaminoethyl, 3-dimethylaminopropyl, 2-sulfonamidoethyl, 2-carboxyethyl, and the like.

The term "alkylene" refers to a diradical of a branched or unbranched saturated hydrocarbon chain, preferably having from 1 to 40 carbon atoms, more preferably 1 to 10 carbon atoms and even more preferably 1 to 6 carbon atoms.

15 This term is exemplified by groups such as methylene (-CH₂-), ethylene (-CH₂CH₂-), the propylene isomers (e.g., -CH₂CH₂CH₂- and -CH(CH₃)CH₂-) and the like.

The term "substituted alkylene" refers to an alkylene group, as defined above, having from 1 to 5 substituents, and preferably 1 to 3 substituents, selected
20 from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocycloxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocycloxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-
25 aryl, -SO-heteroaryl, -SO₂-alkyl, -SO₂-aryl, -SO₂-heteroaryl, -SO₂-substituted alkyl, -SO₂-aryl and -SO₂-heteroaryl. Additionally, such substituted alkylene groups include those where 2 substituents on the alkylene group are fused to form one or more cycloalkyl, substituted cycloalkyl,

cycloalkenyl, substituted cycloalkenyl, aryl, heterocyclic or heteroaryl groups fused to the alkylene group. Preferably such fused groups contain from 1 to 3 fused ring structures.

The term "alkylaminoalkyl", "alkylaminoalkenyl" and "alkylaminoalkynyl"

- 5 refers to the groups R^aNHR^b - where R^a is alkyl group as defined above and R^b is alkylene, alkenylene or alkynylene group as defined above. Such groups are exemplified by 3-methylaminobutyl, 4-ethylamino-1,1-dimethylbutyn-1-yl, 4-ethylaminobutyn-1-yl, and the like.

The term "alkaryl" or "aralkyl" refers to the groups -alkylene-aryl and -

- 10 substituted alkylene-aryl where alkylene, substituted alkylene and aryl are defined herein. Such alkaryl groups are exemplified by benzyl, phenethyl and the like.

The term "alkoxy" refers to the groups alkyl-O-, alkenyl-O-, cycloalkyl-O-, cycloalkenyl-O-, and alkynyl-O-, where alkyl, alkenyl, cycloalkyl, cycloalkenyl, and alkynyl are as defined herein. Preferred alkoxy groups are alkyl-O- and

- 15 include, by way of example, methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, *tert*-butoxy, *sec*-butoxy, *n*-pentoxy, *n*-hexoxy, 1,2-dimethylbutoxy, and the like.

The term "substituted alkoxy" refers to the groups substituted alkyl-O-, substituted alkenyl-O-, substituted cycloalkyl-O-, substituted cycloalkenyl-O-, and substituted alkynyl-O- where substituted alkyl, substituted alkenyl, substituted

- 20 cycloalkyl, substituted cycloalkenyl and substituted alkynyl are as defined herein.

The term "haloalkoxy" refers to the groups alkyl-O- wherein one or more hydrogen atoms on the alkyl group have been substituted with a halo group and include, by way of examples, groups such as trifluoromethoxy, and the like.

The term "alkylalkoxy" refers to the groups -alkylene-O-alkyl,

- 25 alkylene-O-substituted alkyl, substituted alkylene-O-alkyl, and substituted alkylene-O-substituted alkyl wherein alkyl, substituted alkyl, alkylene and substituted alkylene are as defined herein. Preferred alkylalkoxy groups are alkylene-O-alkyl and include, by way of example, methylenemethoxy (-CH₂OCH₃), ethylenemethoxy (-CH₂CH₂OCH₃), *n*-propylene-*iso*-propoxy

(-CH₂CH₂CH₂OCH(CH₃)₂), methylene-*t*-butoxy (-CH₂-O-C(CH₃)₃), and the like.

The term "alkylthioalkoxy" refers to the group -alkylene-S-alkyl, alkylene-S-substituted alkyl, substituted alkylene-S-alkyl and substituted alkylene-S-substituted alkyl wherein alkyl, substituted alkyl, alkylene and substituted alkylene are as defined herein. Preferred alkylthioalkoxy groups are alkylene-S-alkyl and include, by way of example, methylenethiomethoxy (-CH₂SCH₃), ethylenethiomethoxy (-CH₂CH₂SCH₃), *n*-propylene-*iso*-thiopropoxy (-CH₂CH₂CH₂SCH(CH₃)₂), methylene-*t*-thiobutoxy (-CH₂SC(CH₃)₃), and the like.

The term "alkenyl" refers to a monoradical of a branched or unbranched unsaturated hydrocarbon group preferably having from 2 to 40 carbon atoms, more preferably 2 to 10 carbon atoms and even more preferably 2 to 6 carbon atoms and having at least 1 and preferably from 1-6 sites of vinyl unsaturation. Preferred alkenyl groups include ethenyl (-CH=CH₂), *n*-propenyl (-CH₂CH=CH₂), *iso*-propenyl (-C(CH₃)=CH₂), and the like.

15 The term "substituted alkenyl" refers to an alkenyl group as defined above having from 1 to 5 substituents, and preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocycloxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocycloxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-aryl and -SO₂-heteroaryl.

20 The term "alkenylene" refers to a diradical of a branched or unbranched unsaturated hydrocarbon group preferably having from 2 to 40 carbon atoms, more preferably 2 to 10 carbon atoms and even more preferably 2 to 6 carbon atoms and having at least 1 and preferably from 1-6 sites of vinyl unsaturation. This term is

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exemplified by groups such as ethenylene (-CH=CH-), the propenylene isomers (e.g., -CH₂CH=CH- or -C(CH₃)=CH-), and the like.

The term "substituted alkenylene" refers to an alkenylene group as defined above having from 1 to 5 substituents, and preferably from 1 to 3 substituents,

- 5 selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocycloxy, thiol, thioalkoxy, substituted thioalkoxy,
- 10 aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocycloxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-aryl and -SO₂-heteroaryl. Additionally, such substituted alkenylene groups include those where 2 substituents on the alkenylene group are fused to form one or more cycloalkyl, substituted
- 15 cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heterocyclic or heteroaryl groups fused to the alkenylene group.

The term "alkynyl" refers to a monoradical of an unsaturated hydrocarbon preferably having from 2 to 40 carbon atoms, more preferably 2 to 20 carbon atoms and even more preferably 2 to 6 carbon atoms and having at least 1 and preferably

- 20 from 1-6 sites of acetylene (triple bond) unsaturation. Preferred alkynyl groups include ethynyl (-C≡CH), propargyl (-CH₂C≡CH), and the like.

The term "substituted alkynyl" refers to an alkynyl group as defined above having from 1 to 5 substituents, and preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocycloxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy,

heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-aryl, and -SO₂-heteroaryl.

The term "alkynylene" refers to a diradical of an unsaturated hydrocarbon 5 preferably having from 2 to 40 carbon atoms, more preferably 2 to 10 carbon atoms and even more preferably 2 to 6 carbon atoms and having at least 1 and preferably from 1-6 sites of acetylene (triple bond) unsaturation. Preferred alkynylene groups include ethynylene (-C≡C-), propargylene (-CH₂C≡C-), and the like.

The term "substituted alkynylene" refers to an alkynylene group as defined 10 above having from 1 to 5 substituents, and preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, 15 thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-aryl and -SO₂-heteroaryl.

The term "acyl" refers to the groups HC(O)-, alkyl-C(O)-, substituted alkyl- 20 C(O)-, cycloalkyl-C(O)-, substituted cycloalkyl-C(O)-, cycloalkenyl-C(O)-, substituted cycloalkenyl-C(O)-, aryl-C(O)-, heteroaryl-C(O)- and heterocyclic-C(O)- where alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl, and heterocyclic are as defined herein.

25 The term "acylamino" or "aminocarbonyl" refers to the group -C(O)NRR where each R is independently hydrogen, alkyl, substituted alkyl, aryl, heteroaryl, heterocyclic or where both R groups are joined to form a heterocyclic group (e.g., morpholino) wherein alkyl, substituted alkyl, aryl, heteroaryl, and heterocyclic are as defined herein.

The term "aminoacyl" refers to the group -NRC(O)R where each R is independently hydrogen, alkyl, substituted alkyl, aryl, heteroaryl, or heterocyclic wherein alkyl, substituted alkyl, aryl, heteroaryl, and heterocyclic are as defined herein.

5 The term "aminoacyloxy" or "alkoxycarbonylamino" refers to the group -NRC(O)OR where each R is independently hydrogen, alkyl, substituted alkyl, aryl, heteroaryl, or heterocyclic wherein alkyl, substituted alkyl, aryl, heteroaryl, and heterocyclic are as defined herein.

The term "acyloxy" refers to the groups alkyl-C(O)O-, substituted alkyl-
10 C(O)O-, cycloalkyl-C(O)O-, substituted cycloalkyl-C(O)O-, aryl-C(O)O-, heteroaryl-C(O)O-, and heterocyclic-C(O)O- wherein alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, heteroaryl, and heterocyclic are as defined herein.

The term "aryl" refers to an unsaturated aromatic carbocyclic group of from
15 6 to 20 carbon atoms having a single ring (e.g., phenyl) or multiple condensed (fused) rings (e.g., naphthyl or anthryl). Preferred aryls include phenyl, naphthyl and the like. Unless otherwise constrained by the definition for the aryl substituent, such aryl groups can optionally be substituted with from 1 to 5 substituents, preferably 1 to 3 substituents, selected from the group consisting of acyloxy,
20 hydroxy, thiol, acyl, alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkoxy, substituted alkenyl, substituted alkynyl, substituted cycloalkyl, substituted cycloalkenyl, amino, substituted amino, aminoacyl, acylamino, alkaryl, aryl, aryloxy, azido, carboxyl, carboxylalkyl, cyano, halo, nitro, heteroaryl, heteroaryloxy, heterocyclic, heterocycloxy, aminoacyloxy,
25 oxyacylamino, thioalkoxy, substituted thioalkoxy, thioaryloxy, thioheteroaryloxy, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-aryl, -SO₂-heteroaryl and trihalomethyl. Preferred aryl substituents include alkyl, alkoxy, halo, cyano, nitro, trihalomethyl, and thioalkoxy.

The term "aryloxy" refers to the group aryl-O- wherein the aryl group is as defined above including optionally substituted aryl groups as also defined above.

The term " arylene " refers to the diradical derived from aryl (including substituted aryl) as defined above and is exemplified by 1,2-phenylene, 1,3-

5 phenylene, 1,4-phenylene, 1,2-naphthylene and the like.

The term "amino" refers to the group -NH₂.

The term "substituted amino" refers to the group -NRR where each R is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, cycloalkenyl, 10 substituted cycloalkenyl, alkynyl, substituted alkynyl, aryl, heteroaryl, and heterocyclic provided that both R's are not hydrogen.

The term "carboxyalkyl" or "alkoxycarbonyl" refers to the groups "-C(O)O-alkyl", "-C(O)O-substituted alkyl", "-C(O)O-cycloalkyl", "-C(O)O-substituted cycloalkyl", "-C(O)O-alkenyl", "-C(O)O-substituted alkenyl", 15 "-C(O)O-alkynyl" and "-C(O)O-substituted alkynyl" where alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl and substituted alkynyl alkynyl are as defined herein.

The term "cycloalkyl" refers to cyclic alkyl groups of from 3 to 20 carbon atoms having a single cyclic ring or multiple condensed rings. Such cycloalkyl 20 groups include, by way of example, single ring structures such as cyclopropyl, cyclobutyl, cyclopentyl, cyclooctyl, and the like, or multiple ring structures such as adamantanyl, and the like.

The term "substituted cycloalkyl" refers to cycloalkyl groups having from 1 to 5 substituents, and preferably 1 to 3 substituents, selected from the group 25 consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocycloxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy,

heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-aryl and -SO₂-heteroaryl.

The term "cycloalkenyl" refers to cyclic alkenyl groups of from 4 to 20 carbon atoms having a single cyclic ring and at least one point of internal unsaturation. Examples of suitable cycloalkenyl groups include, for instance, cyclobut-2-enyl, cyclopent-3-enyl, cyclooct-3-enyl, and the like.

The term "substituted cycloalkenyl" refers to cycloalkenyl groups having from 1 to 5 substituents, and preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-aryl and -SO₂-heteroaryl.

The term "halo" or "halogen" refers to fluoro, chloro, bromo and iodo.

The term "heteroaryl" refers to an aromatic group of from 1 to 15 carbon atoms and 1 to 4 heteroatoms selected from oxygen, nitrogen and sulfur within at least one ring (if there is more than one ring). Unless otherwise constrained by the definition for the heteroaryl substituent, such heteroaryl groups can be optionally substituted with 1 to 5 substituents, preferably 1 to 3 substituents, selected from the group consisting of acyloxy, hydroxy, thiol, acyl, alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkoxy, substituted alkenyl, substituted alkynyl, substituted cycloalkyl, substituted cycloalkenyl, amino, substituted amino, aminoacyl, acylamino, alkaryl, aryl, aryloxy, azido, carboxyl, carboxylalkyl, cyano, halo, nitro, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, aminoacyloxy, oxyacylamino, thioalkoxy, substituted thioalkoxy,

thioaryloxy, thioheteroaryloxy, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-aryl, -SO₂-heteroaryl and trihalomethyl. Preferred aryl substituents include alkyl, alkoxy, halo, cyano, nitro, trihalomethyl, and thioalkoxy. Such heteroaryl groups can have a single ring (e.g.,

5 pyridyl or furyl) or multiple condensed rings (e.g., indolizinyl or benzothienyl).

Preferred heteroaryls include pyridyl, pyrrolyl and furyl.

The term "heteroaralkyl" refers to the groups -alkylene-heteroaryl where alkylene and heteroaryl are defined herein. Such heteroaralkyl groups are exemplified by pyridylmethyl, pyridylethyl, indolylmethyl, and the like.

10 The term "heteroaryloxy" refers to the group heteroaryl-O-.

The term "heteroarylene" refers to the diradical group derived from heteroaryl (including substituted heteroaryl), as defined above, and is exemplified by the groups 2,6-pyridylene, 2,4-pyridiylene, 1,2-quinolinylene, 1,8-quinolinylene, 1,4-benzofuranylene, 2,5-pyridnylene, 2,5-indolanyl, and the like.

15 *SND* The term "heterocycle" or "heterocyclic" or refers to a monoradical saturated unsaturated group having a single ring or multiple condensed rings, from 1 to 40 carbon atoms and from 1 to 10 hetero atoms, preferably 1 to 4 heteroatoms, selected from nitrogen, sulfur, phosphorus, and/or oxygen within the ring. Unless otherwise constrained by the definition for the heterocyclic substituent, such heterocyclic

20 groups can be optionally substituted with 1 to 5, and preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy,

25 thioheteroaryloxy, thioheterocycloxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocycloxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-aryl and -SO₂-heteroaryl.

Such heterocyclic groups can have a single ring or multiple condensed rings.

Preferred heterocyclics include morpholino, piperidinyl, and the like.

Examples of nitrogen heteroaryls and heterocycles include, but are not limited to, pyrrole, thiophene, furan, imidazole, pyrazole, pyridine, pyrazine, 5 pyrimidine, pyridazine, indolizine, isoindole, indole, indazole, purine, quinolizine, isoquinoline, quinoline, phthalazine, naphthylpyridine, quinoxaline, quinazoline, cinnoline, pteridine, carbazole, carboline, phenanthridine, acridine, phenanthroline, isothiazole, phenazine, isoxazole, phenoxazine, phenothiazine, imidazolidine, imidazoline, pyrrolidine, piperidine, piperazine, indoline, morpholine, 10 tetrahydrofuranyl, tetrahydrothiophene, and the like as well as N-alkoxy-nitrogen containing heterocycles.

The term "heterocycloxy" refers to the group heterocyclic-O-.

The term "thioheterocycloxy" refers to the group heterocyclic-S-.

The term "heterocyclene" refers to the diradical group formed from a

15 heterocycle, as defined herein, and is exemplified by the groups 2,6-morpholino, 2,5-morpholino and the like.

5/20/2021
"Heteroarylarnino" means a 5 membered aromatic ring wherein one or two ring atoms are N, the remaining ring atoms being C. The heterocycloamino ring may be fused to a cycloalkyl, aryl or heteroaryl ring, and it may be optionally 20 substituted with one or more substituents, preferably one or two substituents, selected from alkyl, substituted alkyl, cycloalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, halo, cyano, acyl, amino, substituted amino, acylamino, -OR (where R is hydrogen, alkyl, alkenyl, cycloalkyl, acyl, aryl, heteroaryl, aralkyl, or heteroaralkyl), or -S(O)_nR [where n is an integer from 0 to 2 and R is hydrogen 25 (provided that n is 0), alkyl, alkenyl, cycloalkyl, amino, heterocyclo, aryl, heteroaryl, aralkyl, or heteroaralkyl]. More specifically the term heterocycloamino includes, but is not limited to, imidazole, pyrazole, benzimidazole and benzpyrazole.

"Heterocycloamino" means a saturated monovalent cyclic group of 4 to 8 ring atoms, wherein at least one ring atom is N and optionally contains one or two additional ring heteroatoms selected from the group consisting of N, O, or S(O) n (where n is an integer from 0 to 2), the remaining ring atoms being C, where one or

5 two C atoms may optionally be replaced by a carbonyl group. The heterocycloamino ring may be fused to a cycloalkyl, aryl or heteroaryl ring, and it may be optionally substituted with one or more substituents, preferably one or two substituents, selected from alkyl, substituted alkyl, cycloalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, halo, cyano, acyl, amino, substituted amino, acylamino,

10 -OR (where R is hydrogen, alkyl, alkenyl, cycloalkyl, acyl, aryl, heteroaryl, aralkyl, or heteroaralkyl), or -S(O) n R [where n is an integer from 0 to 2 and R is hydrogen (provided that n is 0), alkyl, alkenyl, cycloalkyl, amino, heterocyclo, aryl, heteroaryl, aralkyl, or heteroaralkyl]. More specifically the term heterocycloamino includes, but is not limited to, pyrrolidino, piperidino, morpholino, piperazino,

15 indolino, or thiomorpholino. The term heterocycloamino also includes, quinuclidine, 1-azabicyclo[2.2.1]heptyl, 1-azabicyclo[3.2.1]octyl and the derivatives thereof.

The term "oxyacylamino" or "aminocarbonyloxy" refers to the group -OC(O)NRR where each R is independently hydrogen, alkyl, substituted alkyl, aryl, heteroaryl, or heterocyclic wherein alkyl, substituted alkyl, aryl, heteroaryl and heterocyclic are as defined herein.

The term "spiro-attached cycloalkyl group" refers to a cycloalkyl group attached to another ring via one carbon atom common to both rings.

The term "thiol" refers to the group -SH.

25 The term "thioalkoxy" or "alkylthio" refers to the group -S-alkyl.

The term "substituted thioalkoxy" refers to the group -S-substituted alkyl.

The term "thioaryloxy" refers to the group aryl-S- wherein the aryl group is as defined above including optionally substituted aryl groups also defined above.

The term "thioheteroaryloxy" refers to the group heteroaryl-S- wherein the heteroaryl group is as defined above including optionally substituted aryl groups as also defined above.

As to any of the above groups which contain one or more substituents, it is
5 understood, of course, that such groups do not contain any substitution or substitution patterns which are sterically impractical and/or synthetically non-feasible. In addition, the compounds of this invention include all stereochemical isomers arising from the substitution of these compounds.

Unless specified otherwise, all ranges referred to herein include the stated
10 end-point values.

The term "pharmaceutically-acceptable salt" refers to salts which retain biological effectiveness and are not biologically or otherwise undesirable. In many cases, the compounds of this invention are capable of forming acid and/or base salts by virtue of the presence of amino and/or carboxyl groups or groups similar thereto.

15 Pharmaceutically-acceptable base addition salts can be prepared from inorganic and organic bases. Salts derived from inorganic bases, include by way of example only, sodium, potassium, lithium, ammonium, calcium and magnesium salts. Salts derived from organic bases include, but are not limited to, salts of primary, secondary and tertiary amines, such as alkyl amines, dialkyl amines,
20 trialkyl amines, substituted alkyl amines, di(substituted alkyl) amines, tri(substituted alkyl) amines, alkenyl amines, dialkenyl amines, trialkenyl amines, substituted alkenyl amines, di(substituted alkenyl) amines, tri(substituted alkenyl) amines, cycloalkyl amines, di(cycloalkyl) amines, tri(cycloalkyl) amines, substituted cycloalkyl amines, disubstituted cycloalkyl amine, trisubstituted
25 cycloalkyl amines, cycloalkenyl amines, di(cycloalkenyl) amines, tri(cycloalkenyl) amines, substituted cycloalkenyl amines, disubstituted cycloalkenyl amine, trisubstituted cycloalkenyl amines, aryl amines, diaryl amines, triaryl amines, heteroaryl amines, diheteroaryl amines, triheteroaryl amines, heterocyclic amines, diheterocyclic amines, triheterocyclic amines, mixed di- and tri-amines where at

least two of the substituents on the amine are different and are selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl, heterocyclic, and the like. Also included are amines where the two or three

5 substituents, together with the amino nitrogen, form a heterocyclic or heteroaryl group. Examples of suitable amines include, by way of example only, isopropylamine, trimethyl amine, diethyl amine, tri(*iso*-propyl) amine, tri(*n*-propyl) amine, ethanolamine, 2-dimethylaminoethanol, tromethamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine,

10 glucosamine, N-alkylglucamines, theobromine, purines, piperazine, piperidine, morpholine, N-ethylpiperidine, and the like. It should also be understood that other carboxylic acid derivatives would be useful in the practice of this invention, for example, carboxylic acid amides, including carboxamides, lower alkyl carboxamides, dialkyl carboxamides, and the like.

15 Pharmaceutically acceptable acid addition salts may be prepared from inorganic and organic acids. Salts derived from inorganic acids include hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like. Salts derived from organic acids include acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid,

20 maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, *p*-toluene-sulfonic acid, salicylic acid, and the like.

 The term " pharmaceutically-acceptable cation " refers to the cation of a pharmaceutically-acceptable salt.

25 The term "protecting group" or "blocking group" refers to any group which when bound to one or more hydroxyl, thiol, amino or carboxyl groups of the compounds (including intermediates thereof) prevents reactions from occurring at these groups and which protecting group can be removed by conventional chemical or enzymatic steps to reestablish the hydroxyl, thiol, amino or carboxyl group. The

particular removable blocking group employed is not critical and preferred removable hydroxyl blocking groups include conventional substituents such as allyl, benzyl, acetyl, chloroacetyl, thiobenzyl, benzylidine, phenacyl, *t*-butyl-diphenylsilyl and any other group that can be introduced chemically onto a hydroxyl

5 functionality and later selectively removed either by chemical or enzymatic methods in mild conditions compatible with the nature of the product. Preferred removable thiol blocking groups include disulfide groups, acyl groups, benzyl groups, and the like. Preferred removable amino blocking groups include conventional substituents such as *t*-butyloxycarbonyl (*t*-BOC), benzyloxycarbonyl

10 (CBZ), fluorenylmethoxy-carbonyl (FMOC), allyloxycarbonyl (ALOC), and the like which can be removed by conventional conditions compatible with the nature of the product. Preferred carboxyl protecting groups include esters such as methyl, ethyl, propyl, *t*-butyl etc. which can be removed by mild conditions compatible with the nature of the product.

15 The term "optional" or "optionally" means that the subsequently described event, circumstance or substituent may or may not occur, and that the description includes instances where said event or circumstance occurs and instances where it does not.

20 The term "inert organic solvent" or "inert organic solvent" means a solvent which is inert under the conditions of the reaction being described in conjunction therewith including, by way of example only, benzene, toluene, acetonitrile, tetrahydrofuran, dimethylformamide, chloroform, methylene chloride, diethyl ether, ethyl acetate, acetone, methylethyl ketone, methanol, ethanol, propanol, isopropanol, *t*-butanol, dioxane, pyridine, and the like. Unless specified to the

25 contrary, the solvents used in the reactions described herein are inert solvents.

The term "treatment" refers to any treatment of a pathologic condition in a mammal, particularly a human, and includes:

(i) preventing the pathologic condition from occurring in a subject which may be predisposed to the condition but has not yet been diagnosed with the

condition and, accordingly, the treatment constitutes prophylactic treatment for the disease condition;

- (ii) inhibiting the pathologic condition, i.e., arresting its development;
- (iii) relieving the pathologic condition, i.e., causing regression of the 5 pathologic condition; or
- (iv) relieving the conditions mediated by the pathologic condition.

The term "pathologic condition which is modulated by treatment with a ligand" covers all disease states (i.e., pathologic conditions) which are generally acknowledged in the art to be usefully treated with a ligand for the muscarinic

10 receptors in general, and those disease states which have been found to be usefully treated by a compound of the invention. Such disease states include, by way of example only, the treatment of a mammal afflicted with chronic obstructive pulmonary disease, chronic bronchitis, irritable bowel syndrome, urinary incontinence, and the like.

15 The term "therapeutically effective amount" refers to that amount of a compound which is sufficient to effect treatment, as defined above, when administered to a mammal in need of such treatment. The therapeutically effective amount will vary depending upon the subject and disease condition being treated, the weight and age of the subject, the severity of the disease condition, the manner 20 of administration and the like, which can readily be determined by one of ordinary skill in the art.

The term "linker", identified by the symbol 'X' refers to a group or groups that covalently attaches L_1 and L_2 . Additionally, the linker can be either a chiral or achiral molecule. The term "linker" does not, however, extend to cover solid inert 25 supports such as beads, glass particles, fibers, and the like. But it is understood that the compounds of this invention can be attached to a solid support if desired. For example, such attachment to solid supports can be made for use in separation and purification processes and similar applications.

"Pro-drugs" means any compound which releases an active parent drug according to Formula (I) in vivo when such prodrug is administered to a mammalian subject. Prodrugs of a compound of Formula (I) are prepared by modifying functional groups present in the compound of Formula (I) in such a way

5 that the modifications may be cleaved in vivo to release the parent compound.

Prodrugs include compounds of Formula (I) wherein a hydroxy, amino, or sulfhydryl group in compound (I) is bonded to any group that may be cleaved in vivo to regenerate the free hydroxyl, amino, or sulfhydryl group, respectively.

Examples of prodrugs include, but are not limited to esters (e.g., acetate, formate,

10 and benzoate derivatives), carbamates (e.g., N,N-dimethylaminocarbonyl) of hydroxy functional groups in compounds of Formula (I), and the like.

While the broadest definition of this invention is set forth in the Summary of the Invention, certain compounds of Formula (I) may be preferred. Specific and preferred values listed herein for radicals, substituents, and ranges, are for

15 illustration only; they do not exclude other defined values or other values within defined ranges for the radicals and substituents

A preferred value for A is phenyl or pyridine

A preferred value for R¹ is hydrogen, methyl, or ethyl.

Another preferred value for R¹ is hydrogen.

20 A preferred value for R² is pyrrolyl, pyridinyl, or imidazolyl.

Another preferred value for R² is phenyl.

A preferred value for V is -CH- or -NR⁴- (wherein R⁴ is hydrogen, alkyl, substituted alkyl, aryl, or heteroaryl).

A preferred value for R³ is hydrogen or alkyl

25 A preferred value for R⁵ is hydrogen, alkyl, aryl, aralkyl, heteroaralkyl, or a covalent bond attaching (a) to a linker

Another preferred value for R⁵ is hydrogen, methyl, phenyl optionally substituted with alkyl, alkoxy, halo, hydroxy, carboxy, or amino, benzyl optionally substituted with alkyl, alkoxy, halo, hydroxy, carboxy, or amino.

A preferred value for R⁶, R⁷, and R⁸ independent of each other is hydrogen, alkyl, nitro, hydroxy, or amino.

A preferred value for K is alkylene having from 1 to 10 carbon atoms.

A preferred value for K is alkylene having from 1 to 5 carbon atoms.

5 A preferred value for K is a bond or a methylene group.

A preferred value for K" is a bond.

A preferred value for R^x is alkyl, alkenyl, or alkynyl, each optionally substituted with 1 to 5 alkoxy or fluoro substituents.

Another preferred value for R^x is (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, each optionally substituted with 1 to 3 methoxy, ethoxy or fluoro substituents.

Another preferred value for R^x is (C₁-C₆)alkyl optionally substituted with 1 to 3 methoxy, ethoxy, or fluoro substituents.

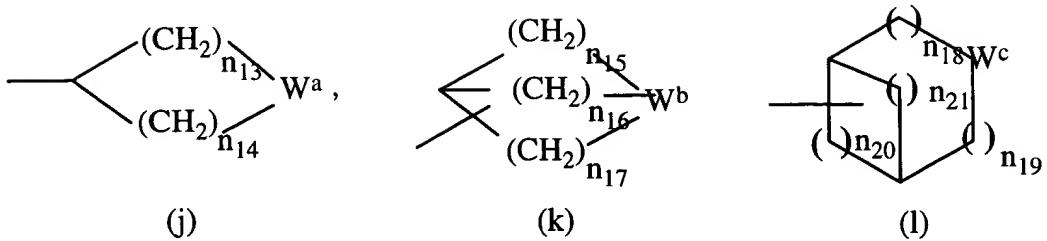
Another preferred value for R^x is methyl, ethyl, propyl, isopropyl, butyl, isobutyl or secbutyl, optionally substituted with methoxy or ethoxy or with 1 to 3 or fluoro substituents.

Another preferred value for R^x is methyl, ethyl, methoxymethyl, ethoxymethyl, methoxyethyl, ethoxyethyl, fluoromethyl, difluoromethyl trifluoromethyl, trifluoromethoxymethyl, formyl, or acetyl.

20 A more preferred value for R^x is methyl, ethyl, methoxymethyl, fluoromethyl, difluoromethyl, or trifluoromethyl.

A preferred value for B is a heterocycloamino group which attaches (a) to a linker.

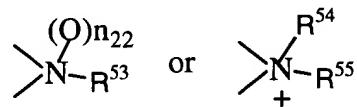
Another preferred value for B is a formula selected from a group consisting 25 of formula (j), formula (k), and formula (l):



wherein:

5 n_{13} and n_{14} are, independently of each other, an integer of from 0 to 4
 provided that $n_{13}+n_{14}$ is an integer of from 3 to 5;
 n_{15} and n_{17} are, independently of each other, an integer of from 0 to 4
 provided that $n_{15}+n_{17}$ is an integer of from 3 to 5;
 n_{16} is an integer of from 0 to 3 provided that $n_{15} + n_{16}$ is an integer of from 3
 to 5;
 10 n_{18} , n_{19} and n_{20} are, independently of each other, an integer of from 0 to 3
 provided that $n_{18}+ n_{19} + n_{20}$ is 2 or 3;
 n_{21} is an integer of from 1 to 3;
 W^a and W^c are, independently of each other:

15



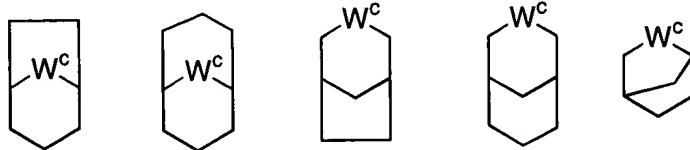
where:

20 n_{22} is 0 or 1;
 R^{53} and R^{54} are, independently of each other, hydrogen, alkyl, alkenyl,
 alkynyl, cycloalkylalkyl, aralkyl, or heterocyclalkyl or a covalent bond attaching
 (a) to a linker;
 R^{55} is alkyl, alkenyl or alkynyl; and

W^b is -N(O)n₂₃ or -N⁺-R⁵⁶ where n₂₃ is 0 or 1, and R⁵⁶ is alkyl, alkenyl, alkynyl, or aralkyl, or a covalent bond attaching (a) to a linker; provided that a carbon other than a bridge head carbon is bonded to B".

Another preferred value for B is a ring represented by the following general

5 formulae:



wherein a carbon atom other than a bridge head carbon is bound to B"; and W^c is as defined above.

A more preferred value for B is pyrrolidine, piperidine, or hexahydroazepine attaching (a) to a linker.

10 Another more preferred value for B is piperidine wherein the nitrogen atom of said piperidine attaches (a) to a linker.

Another more preferred value for B is piperidin-4-yl wherein the nitrogen at the 1 position optionally attaches (a) to a linker.

15 Another more preferred value for B is quinuclidine, 1-azabicyclo[2.2.1]-heptyl, or 1-azabicyclo[3.2.1]octyl attaching (a) to a linker, wherein a carbon other than a bridge head carbon is bound to B".

A preferred value for B taken together with R^x is 4-methylpiperidine-1,4-diyil.

20 A preferred value for D" is -(CH₂)n₄₃- where n₄₃ is an integer of from 1-10, preferably 2-8, more preferably 2-4. Another preferred value for n₄₃ is an integer of from 3-10.

25 A preferred value for D is -NR³¹R³² or -N⁺(R³³R³⁴R³⁵)M- where R³¹, R³³, and R³⁴ are, independently of each other, hydrogen or methyl, and R³² and R³⁵ represent a covalent bond attaching (b) to a linker. More preferably R³¹, R³³, and R³⁴ methyl, and R³² and R³⁵ represent a covalent bond attaching (b) to a linker.

A preferred value for R^{27} is hydrogen.

A preferred value for R^{28} is hydrogen.

A preferred value for R^{29} and R^{30} independently is hydrogen; or one of R^{27} , R^{28} , R^{29} , or R^{30} together with the adjacent group forms a methylenedioxy or

5 ethylenedioxy group.

A preferred value for n_{11} is 1.

A preferred value for n_{12} is 6.

A preferred value for F is $-O-$.

A preferred value for F'' is a covalent bond, $-OR^{43}$, $-NR^{42}R^{43}$ wherein R^{42} is

10 hydrogen or alkyl, or $-N^+(R^{43}R^{44}R^{45})$ wherein R^{44} and R^{45} are alkyl, and R^{43} is a covalent bond attaching (c) to a linker.

A preferred value for F'' is $-O-$, $-NH-$, $N(CH_3)-$ or $-N(CH_3)_2-$

A more preferred value for F'' is $-NH-$, $N(CH_3)-$ or $-N(CH_3)_2-$ wherein the nitrogen atom attaches (c) to a linker.

15 A preferred value for R^{36} is hydrogen.

Preferably R^{37} is ortho to the $-(CHR^{38})-$ group and is hydrogen or alkoxy.

More preferably R^{37} is ortho to the $-(CHR^{38})-$ group and is methoxy.

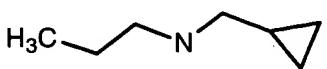
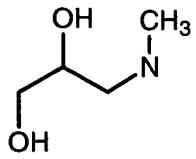
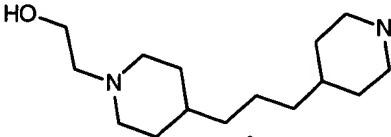
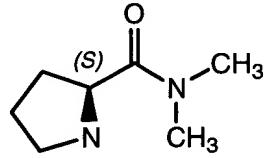
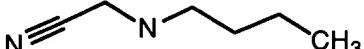
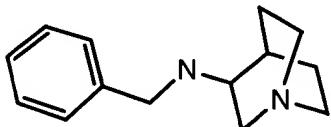
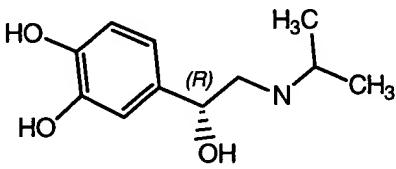
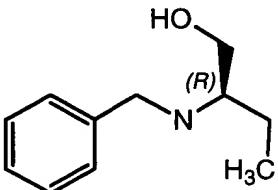
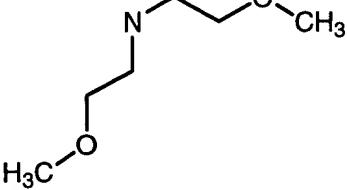
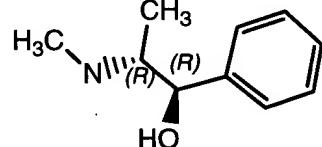
Preferably R^{38} is hydrogen.

Preferably R^{39} is hydrogen.

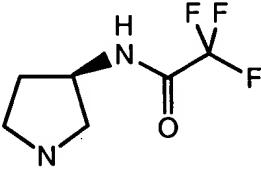
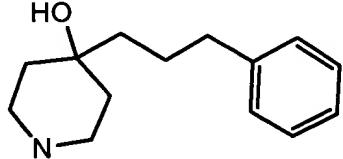
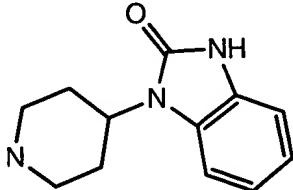
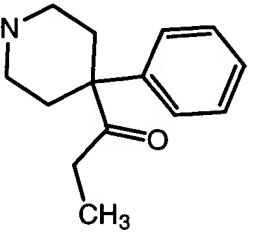
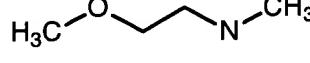
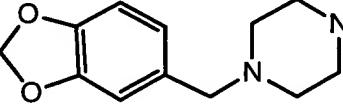
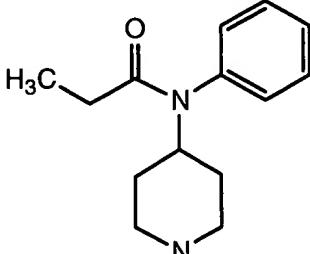
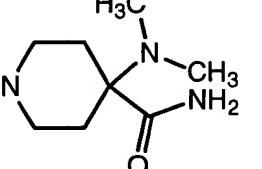
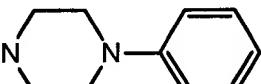
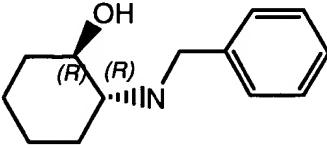
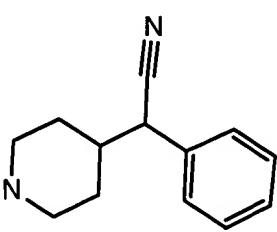
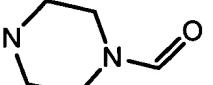
20 Preferably L_2 is a group of formula (d) wherein: R^{46} is alkyl or substituted alkyl; R^{47} is alkyl, substituted alkyl, or heterocycle; or R^{46} and R^{47} together with the nitrogen atom to which they are attached form heterocycle.

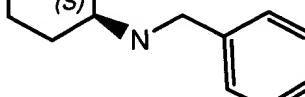
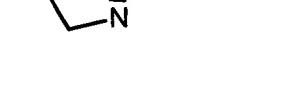
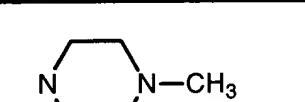
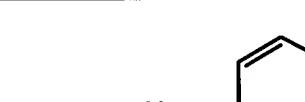
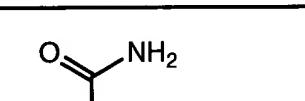
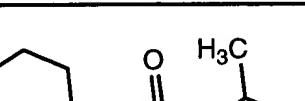
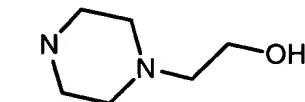
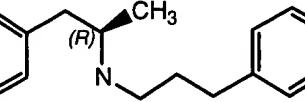
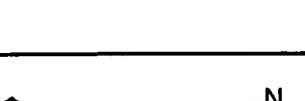
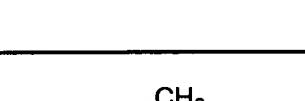
25 Preferably, L_2 is a group of formula A1-A241 as shown in the following table. L_2 is preferably linked to X through a non-aromatic nitrogen atom (e.g. a secondary amino nitrogen) of L_2 .

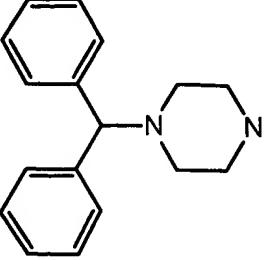
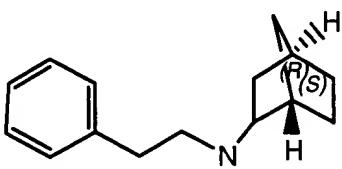
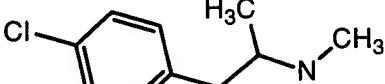
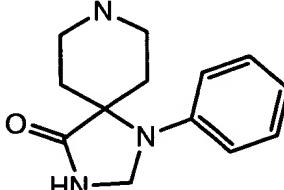
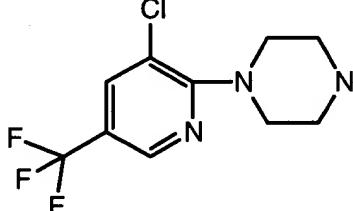
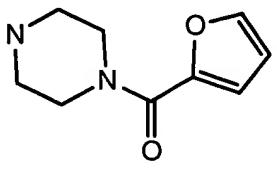
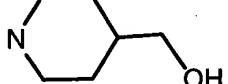
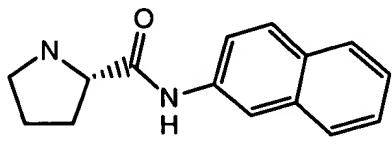
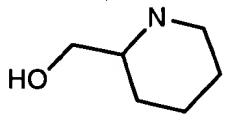
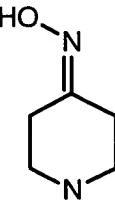
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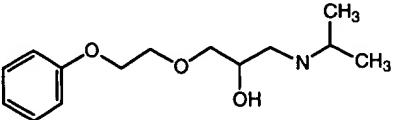
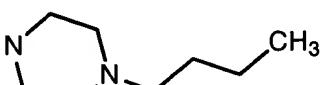
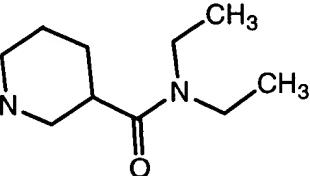
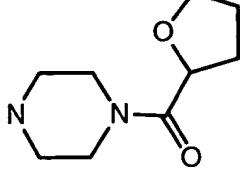
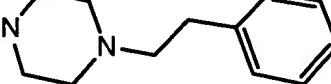
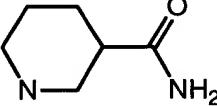
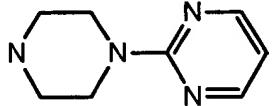
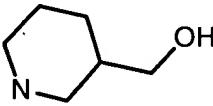
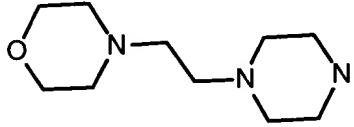
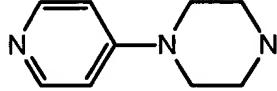
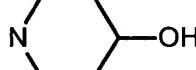
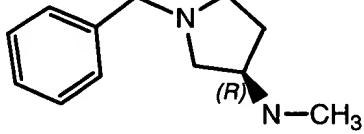
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A5		A6	
A7		A8	
A9		A10	

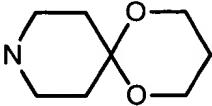
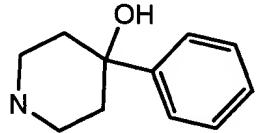
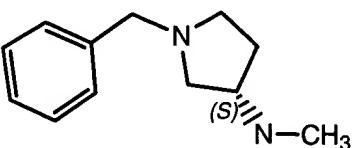
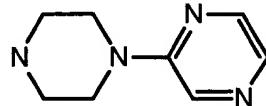
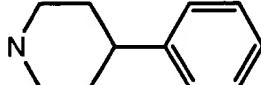
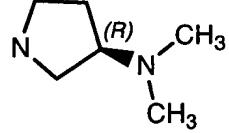
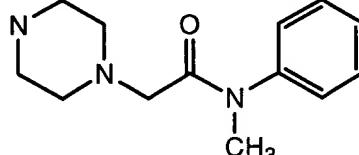
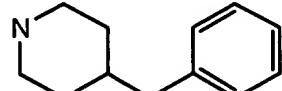
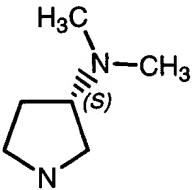
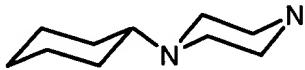
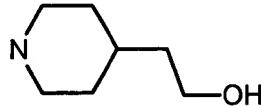
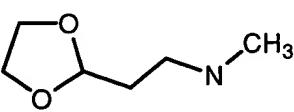
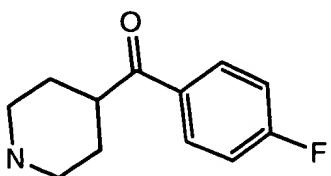
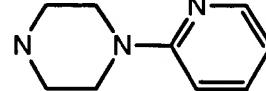
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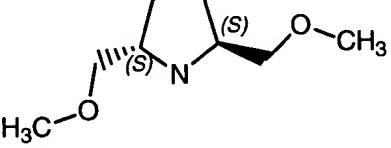
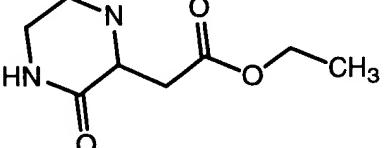
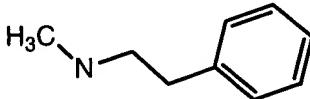
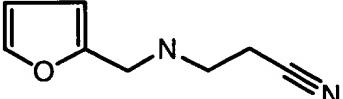
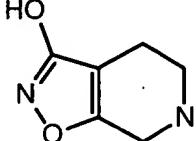
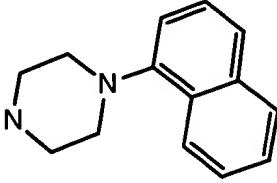
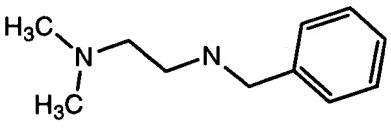
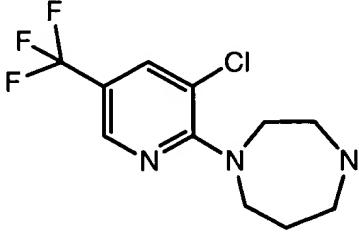
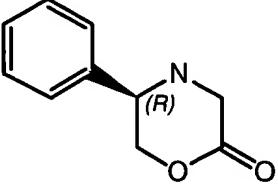
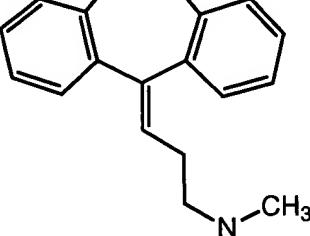
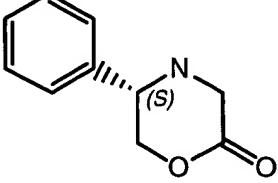
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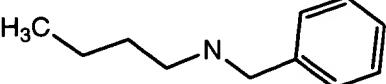
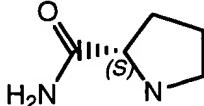
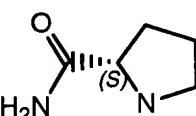
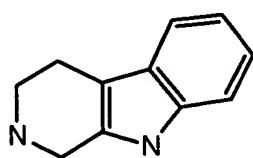
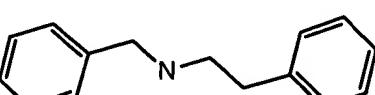
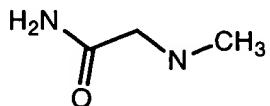
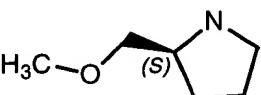
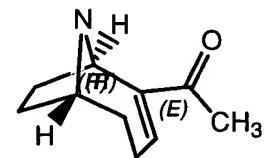
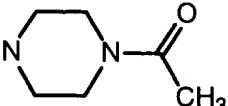
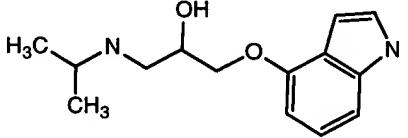
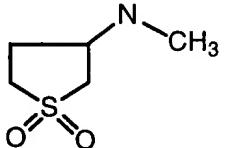
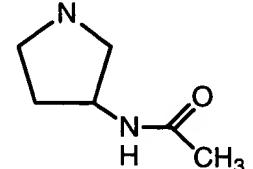
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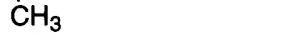
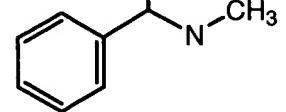
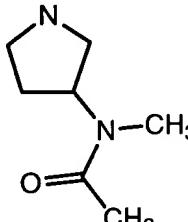
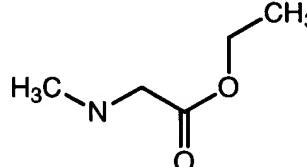
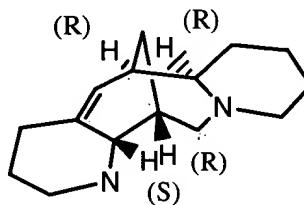
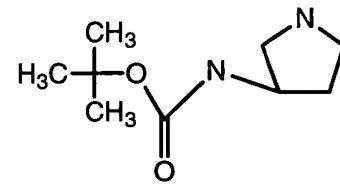
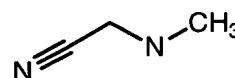
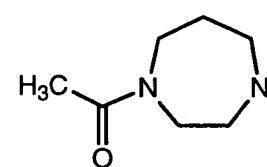
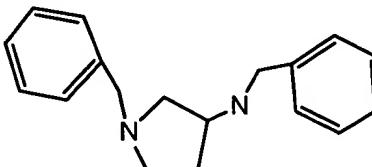
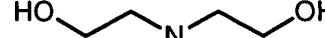
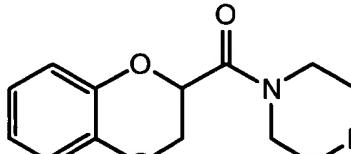
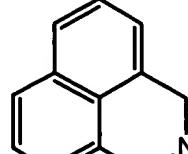
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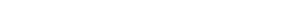
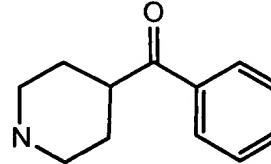
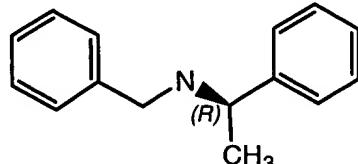
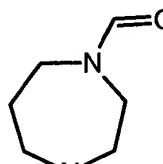
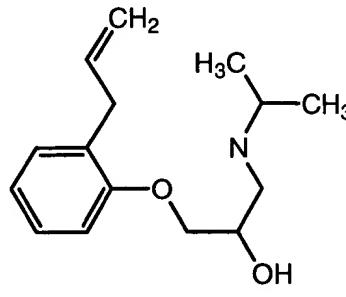
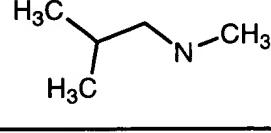
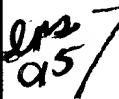
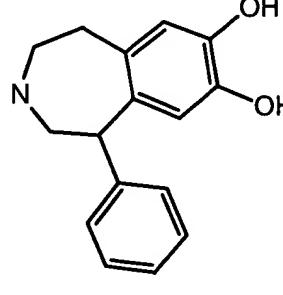
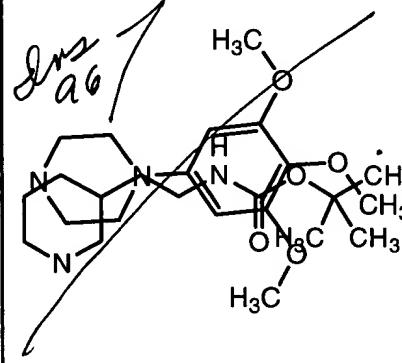
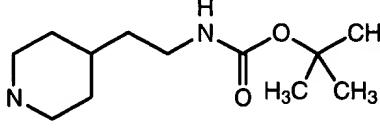
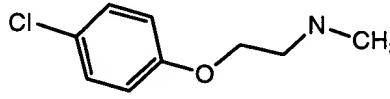
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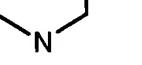
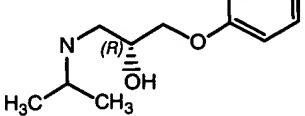
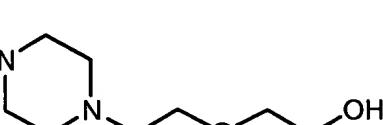
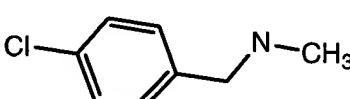
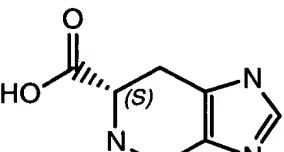
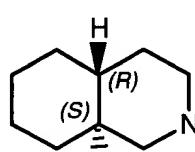
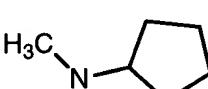
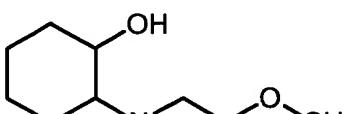
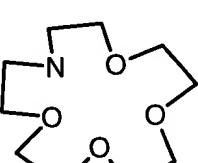
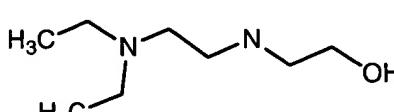
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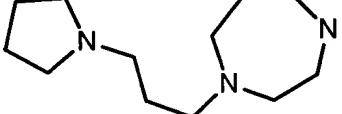
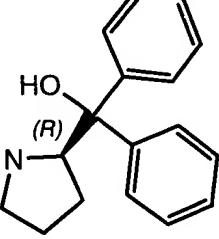
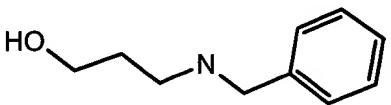
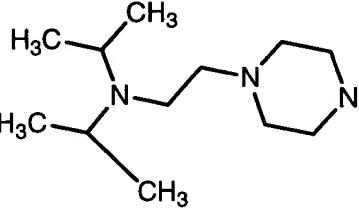
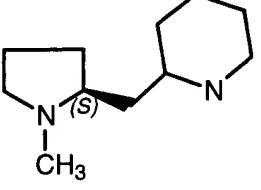
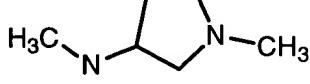
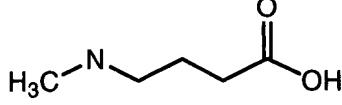
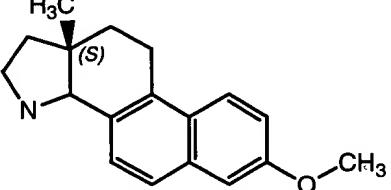
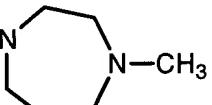
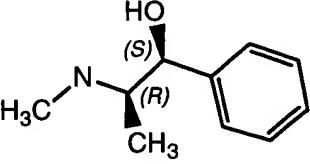
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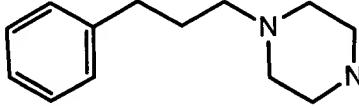
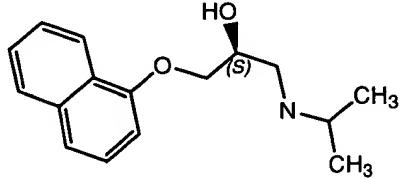
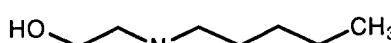
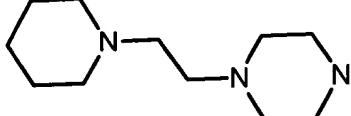
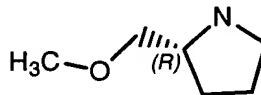
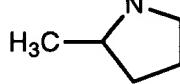
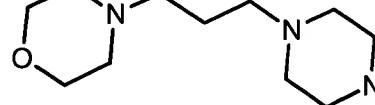
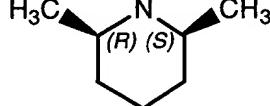
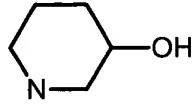
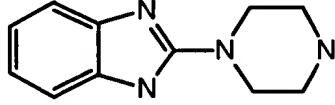
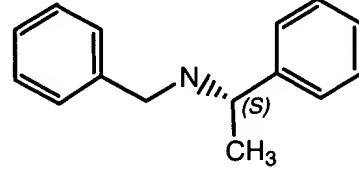
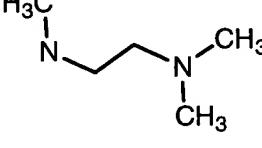
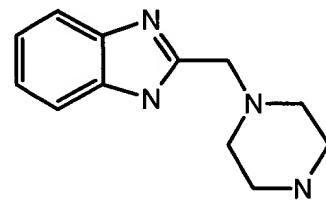
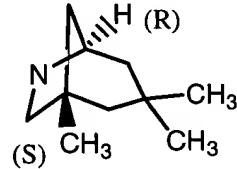
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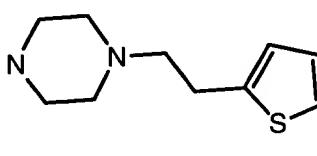
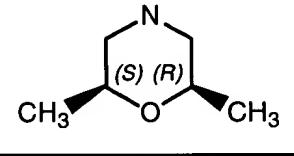
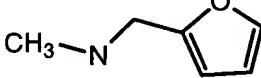
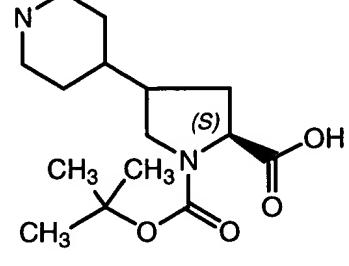
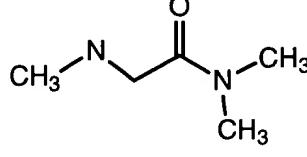
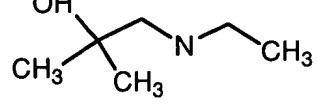
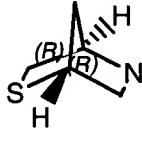
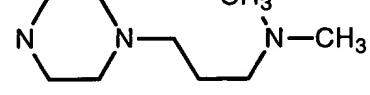
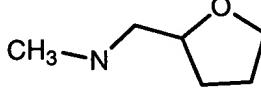
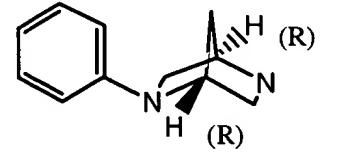
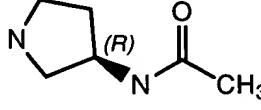
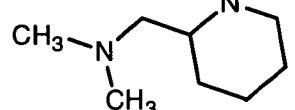
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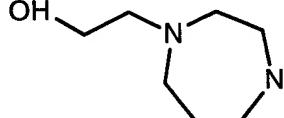
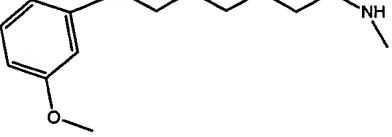
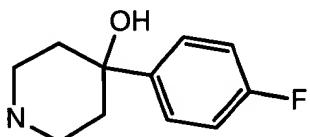
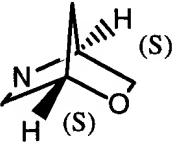
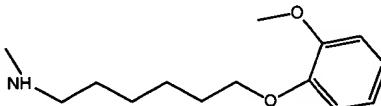
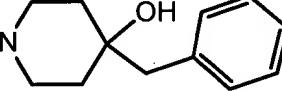
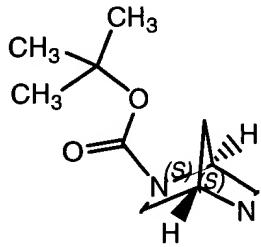
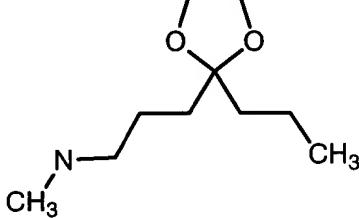
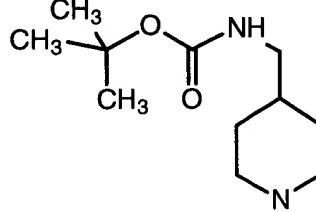
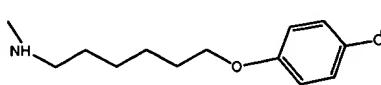
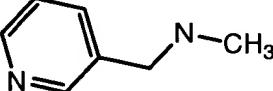
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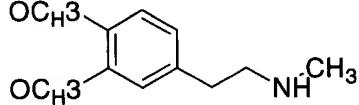
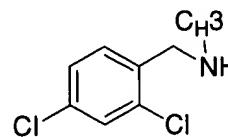
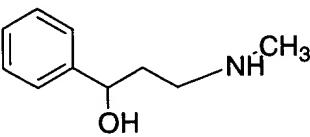
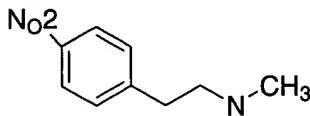
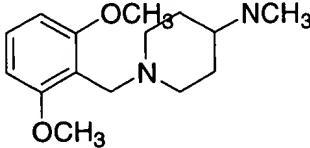
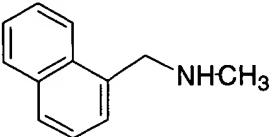
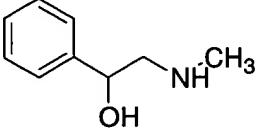
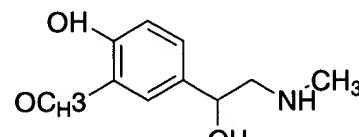
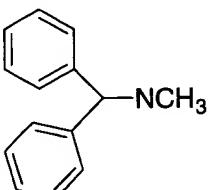
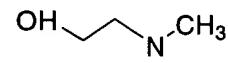
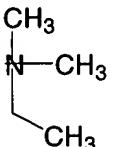
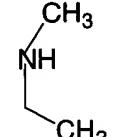
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A175		A176	

A177		A178	
A179		A180	
A181		A182	
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A187		A188	
A189		A190	

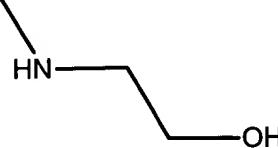
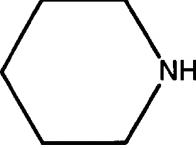
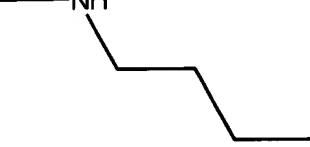
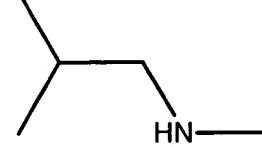
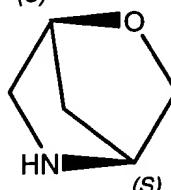
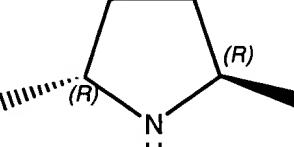
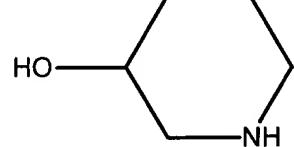
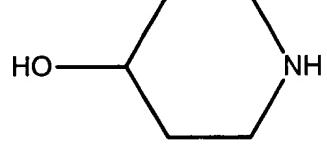
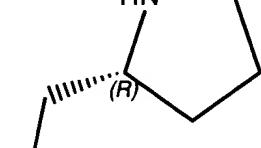
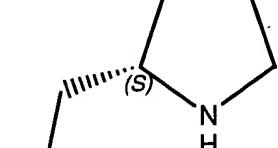
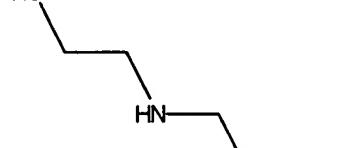
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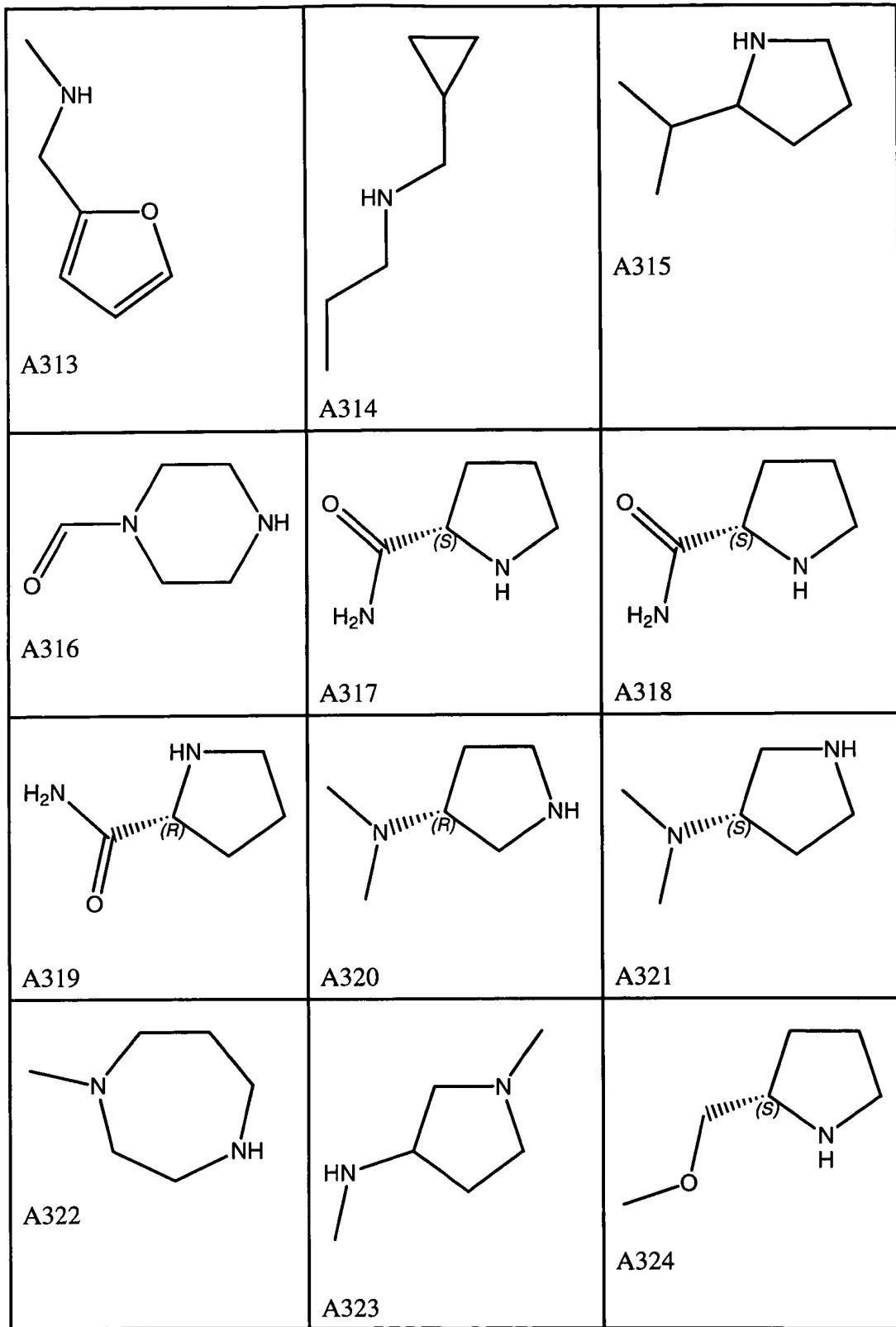
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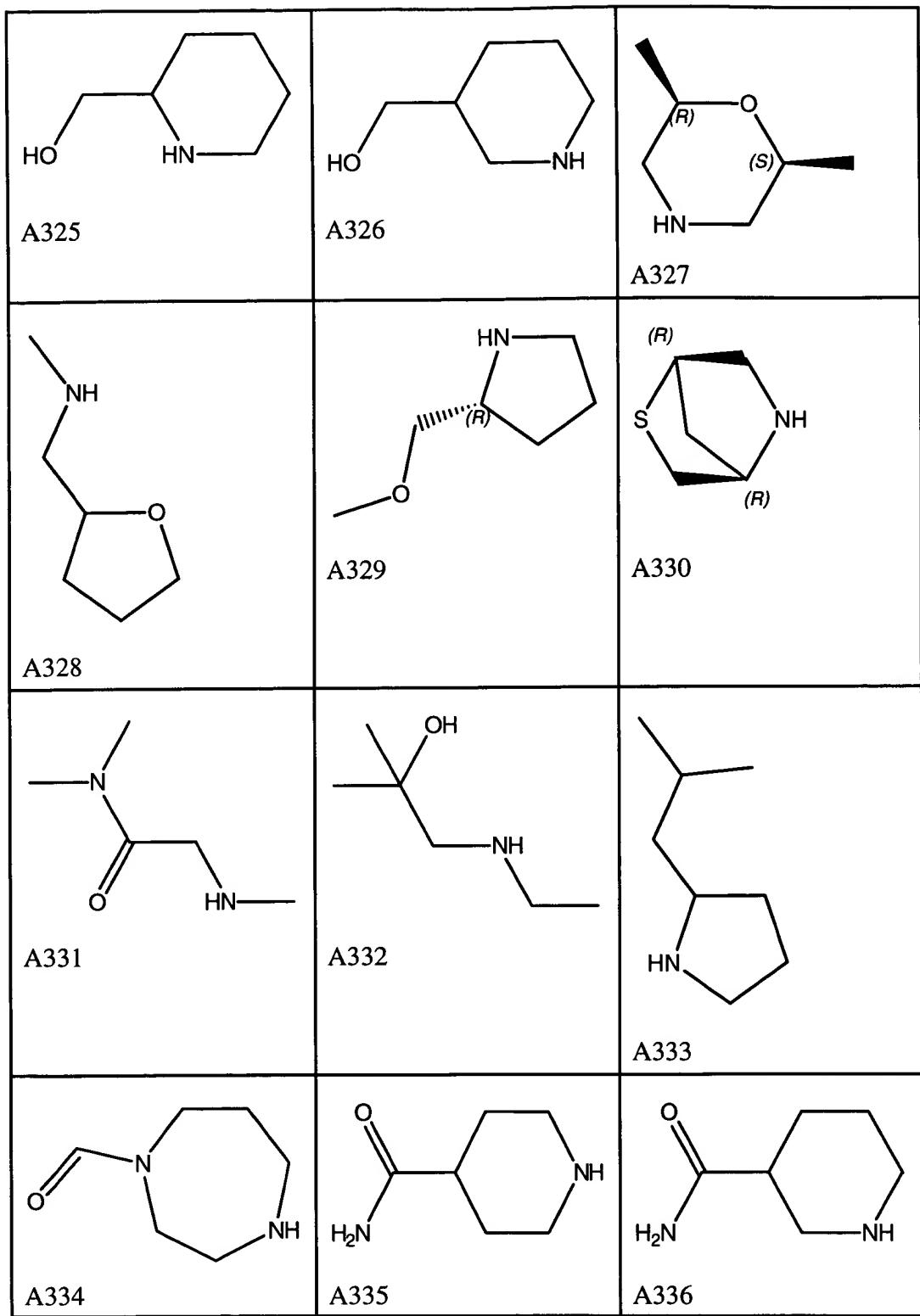
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		A228	

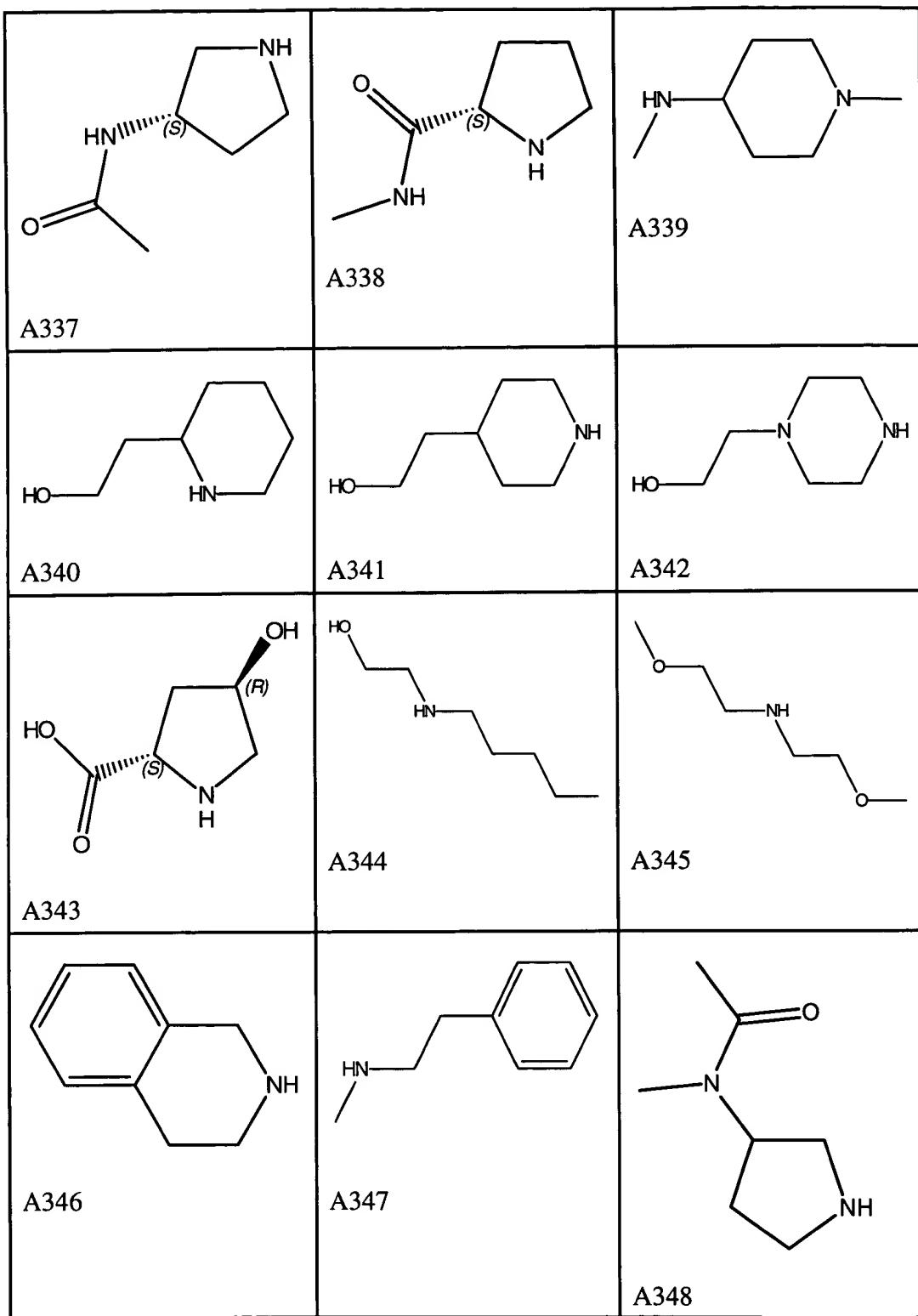
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	A241			

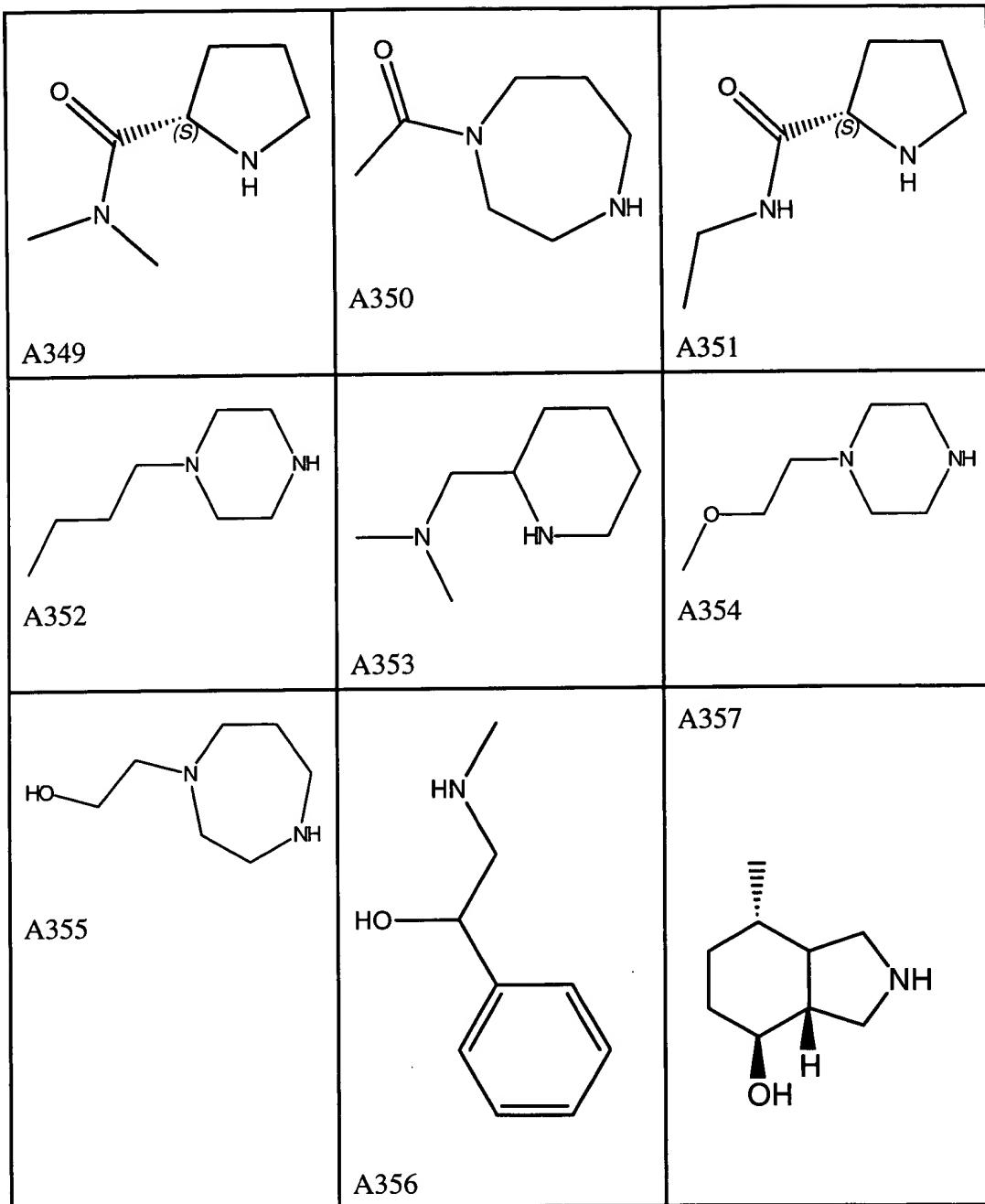
Preferably, L_2 can also be a group of formula A301-A439 as shown in the following table. L_2 is preferably linked to X through a non-aromatic nitrogen atom (e.g. a secondary amino nitrogen) of L_2 .

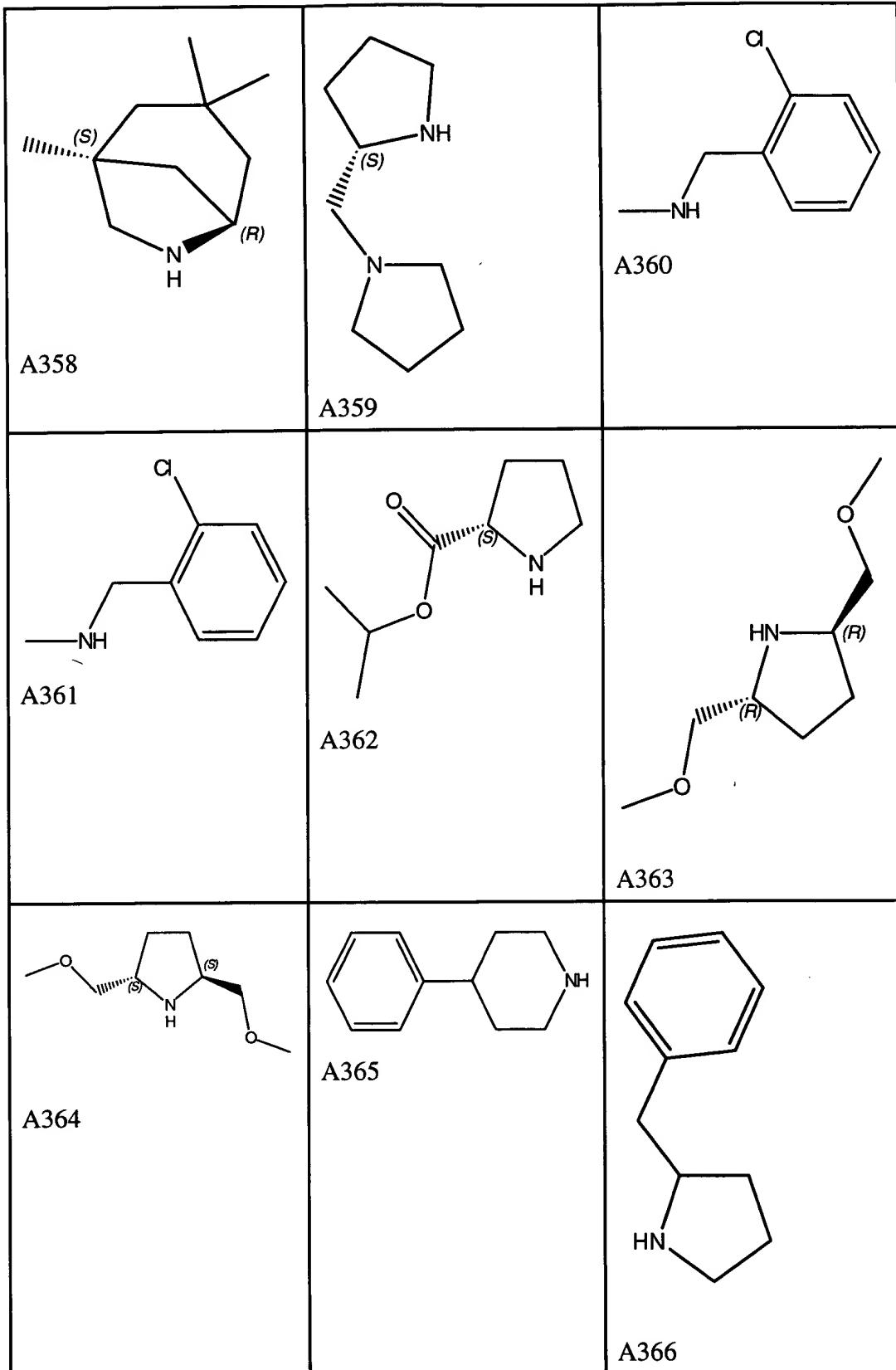
 A301	 A302	 A303
 A304	 A305	 A306
 A307	 A308	 A309
 A310	 A311	 A312

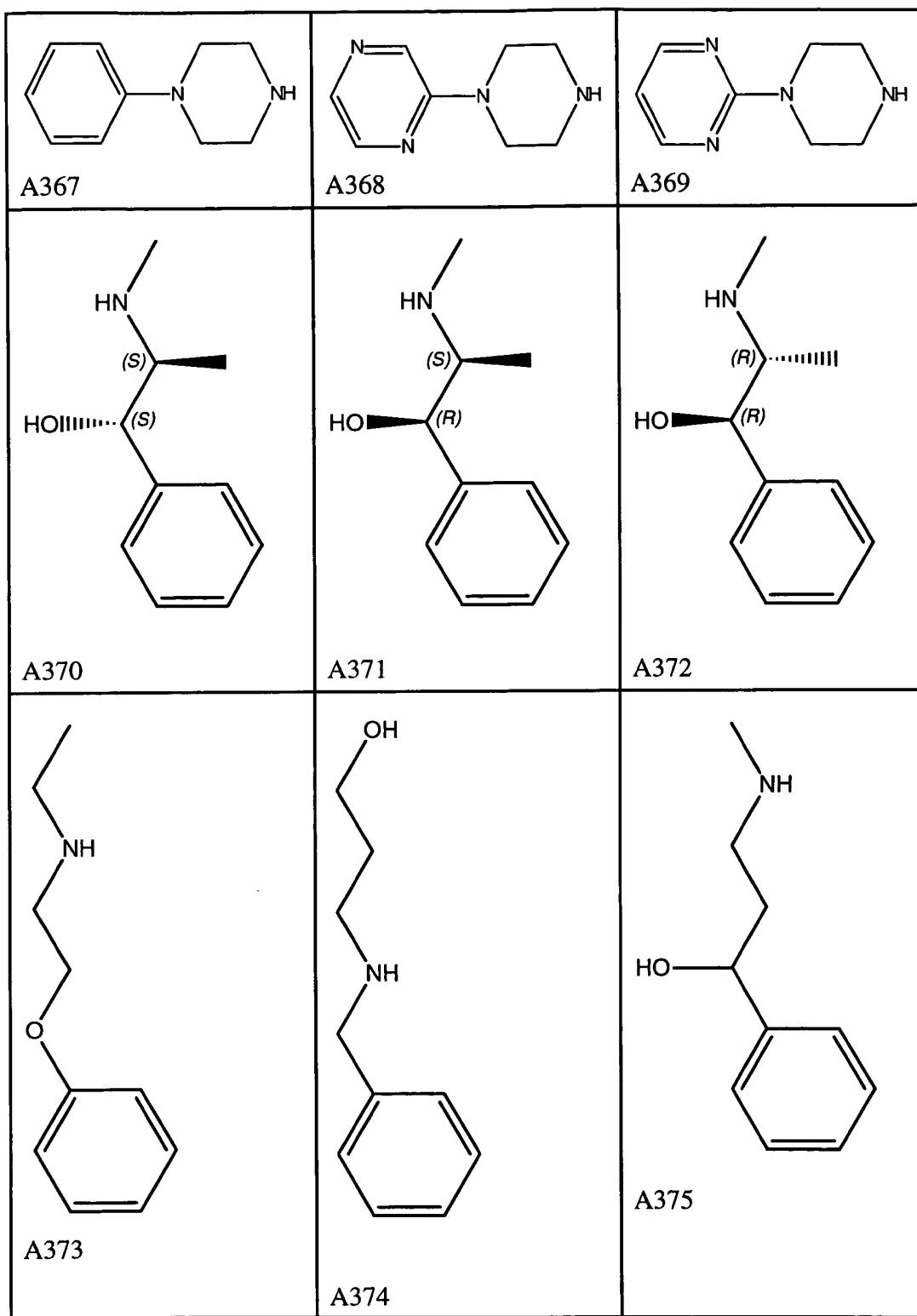


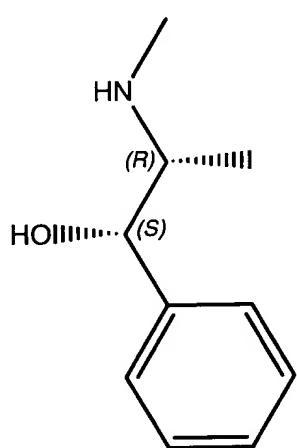




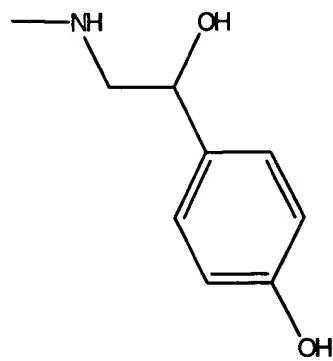




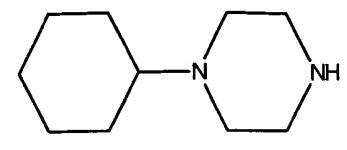




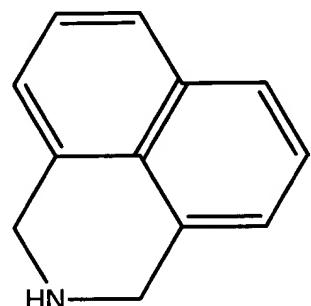
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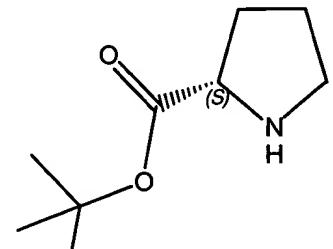
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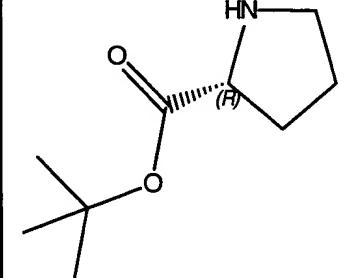
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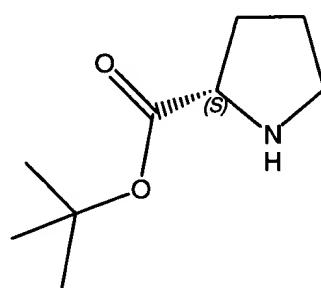
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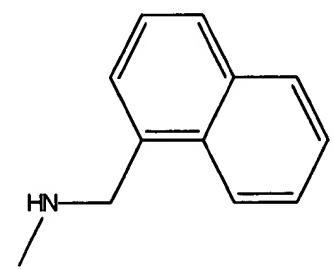
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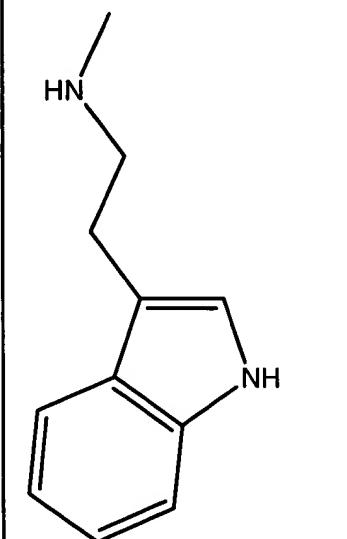
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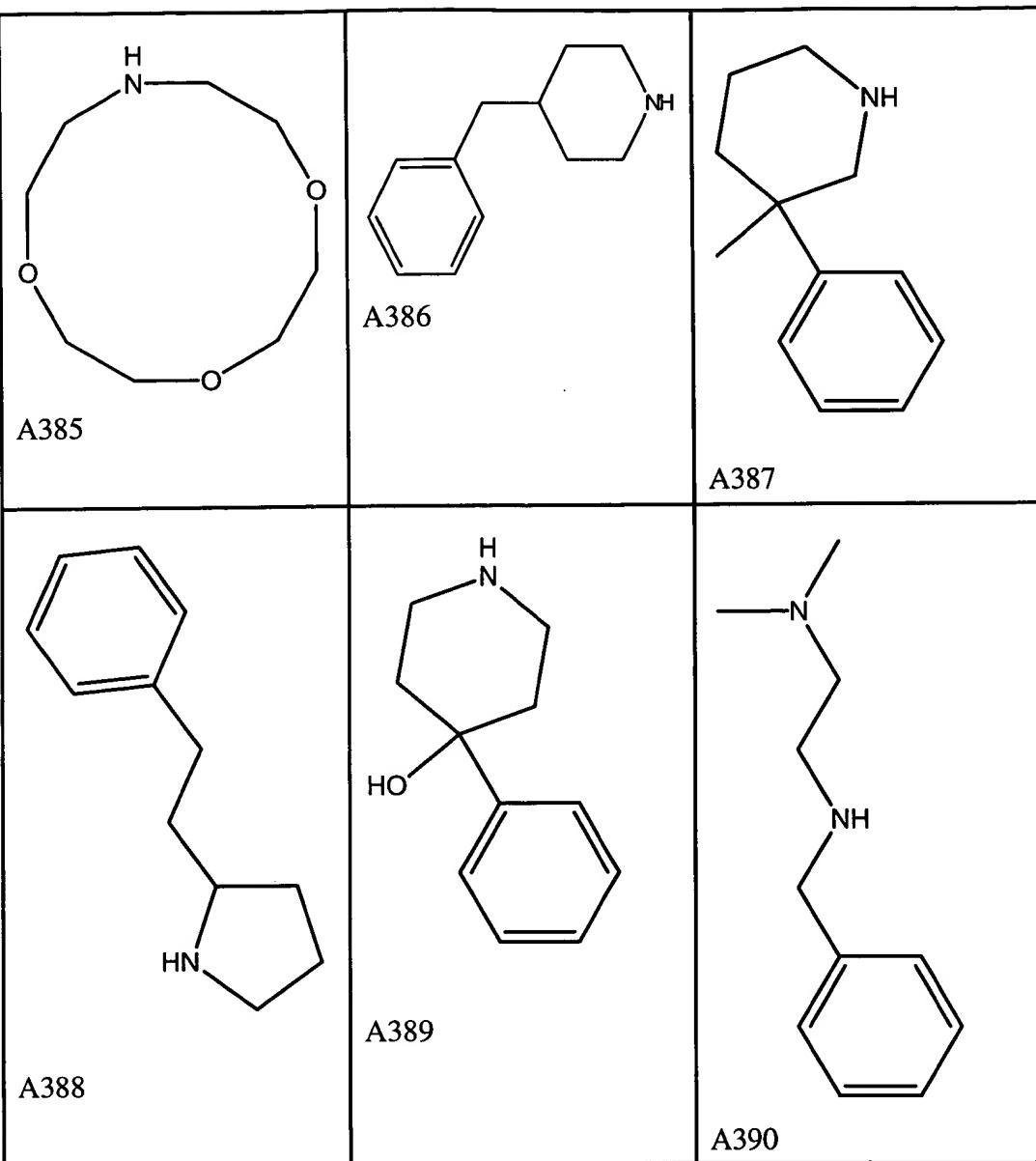
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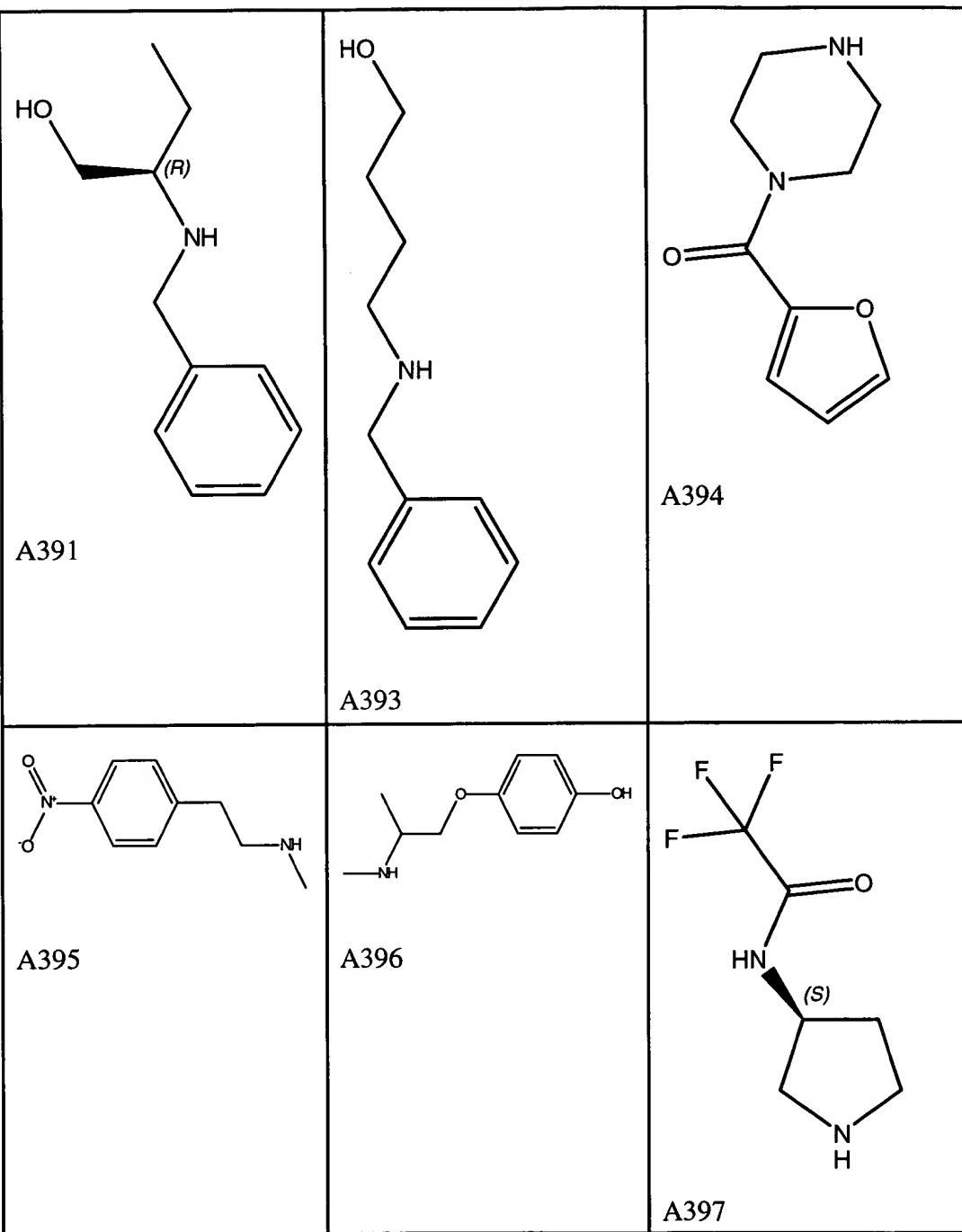


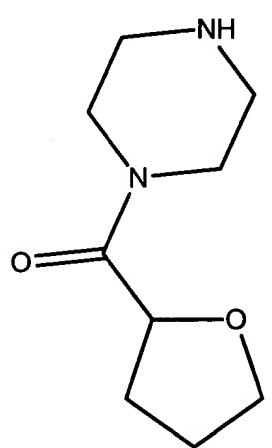
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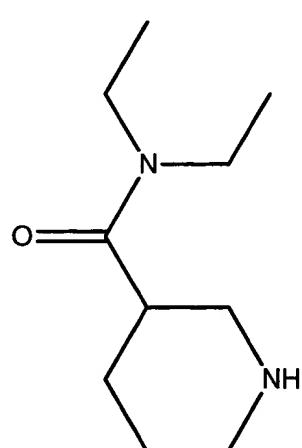
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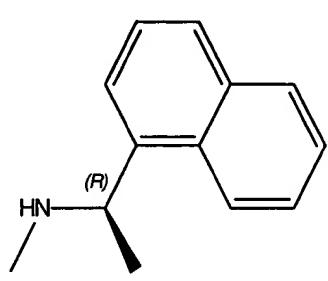




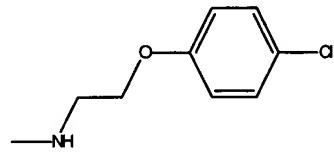
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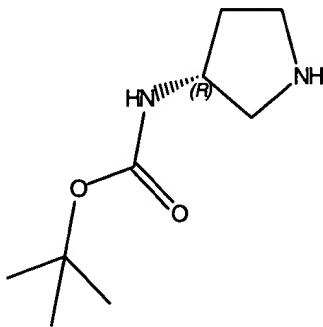
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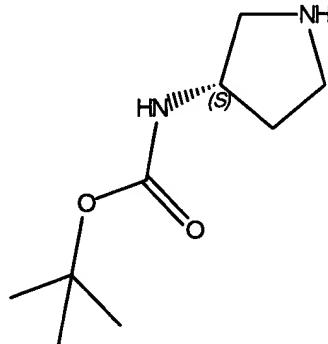
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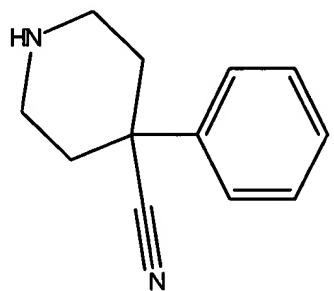
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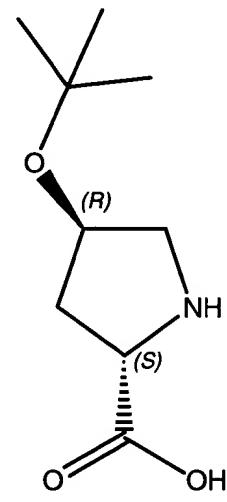
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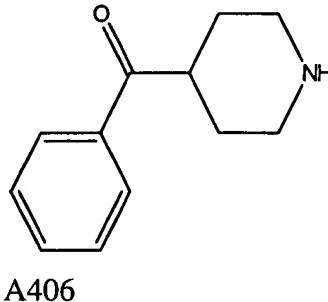
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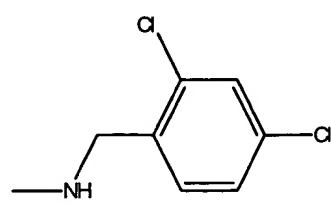
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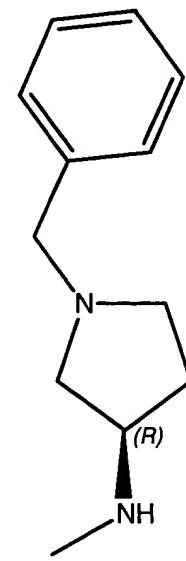
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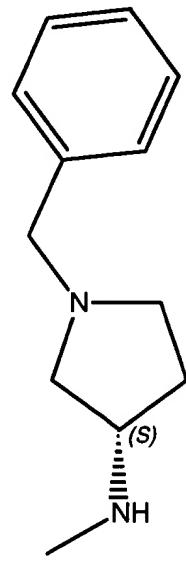
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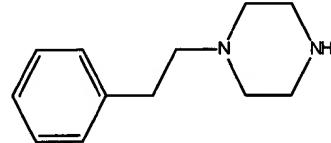
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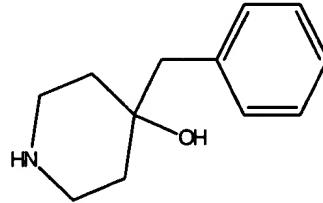
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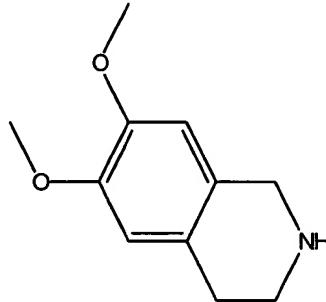
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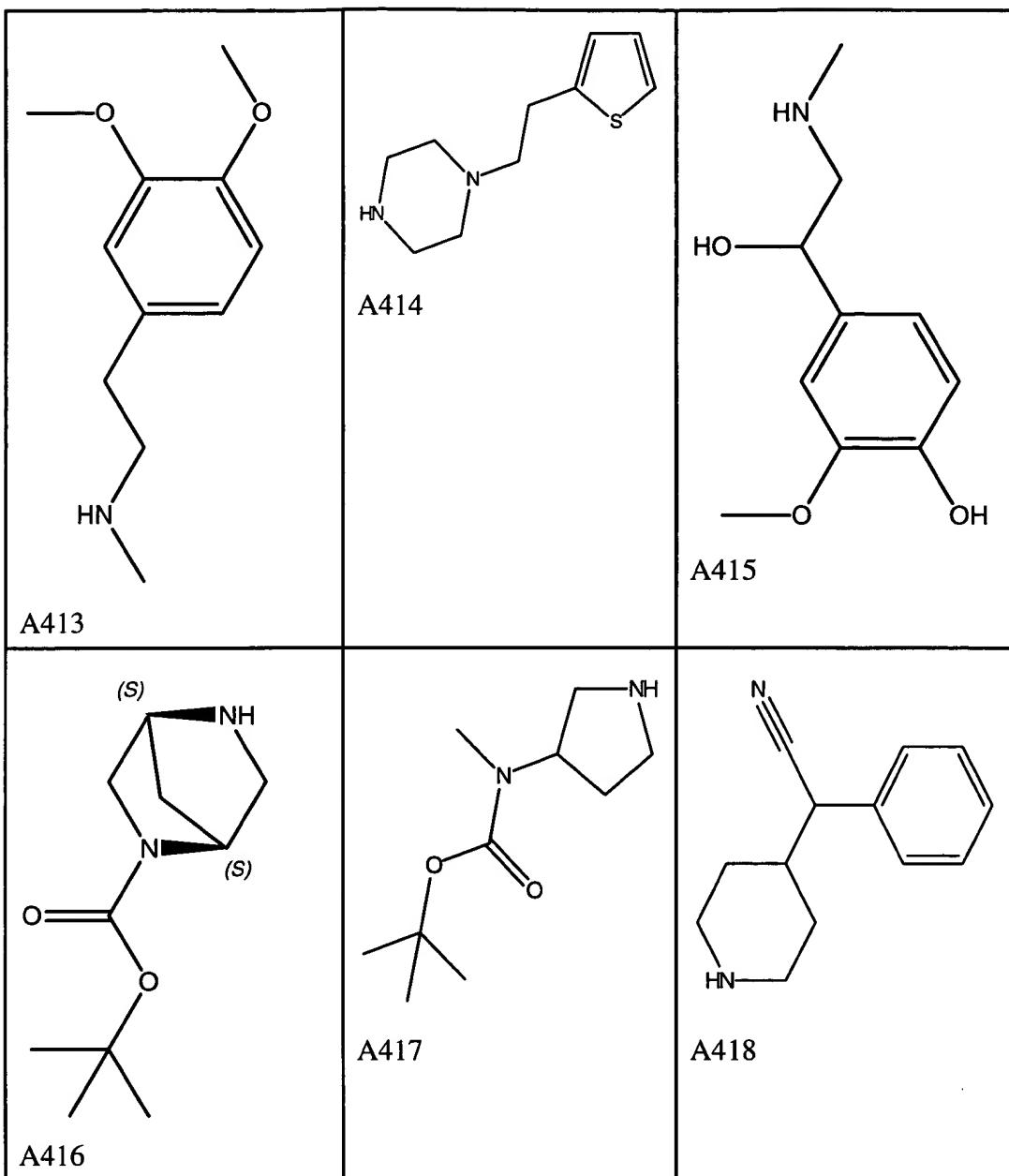
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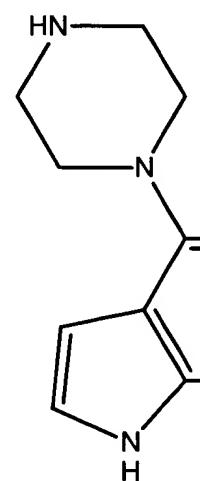


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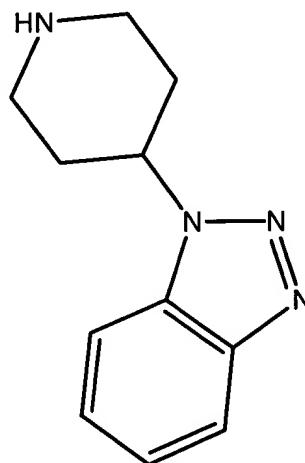


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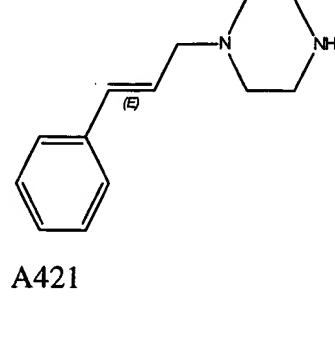




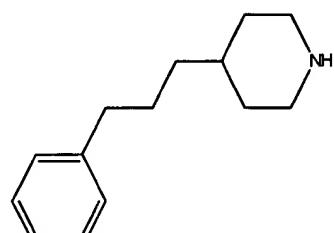
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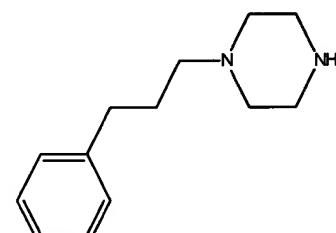
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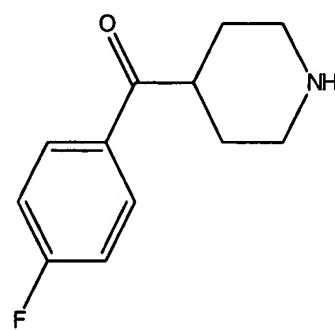
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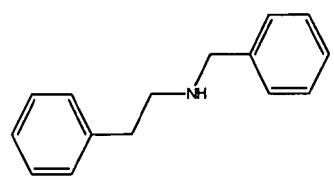
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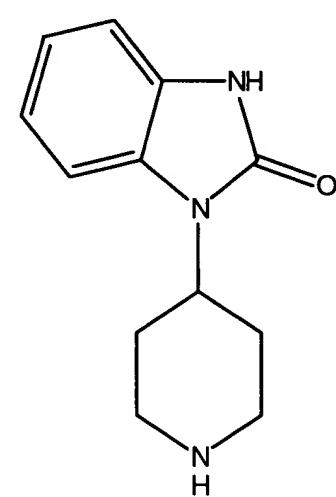
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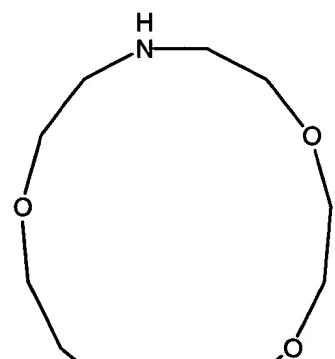
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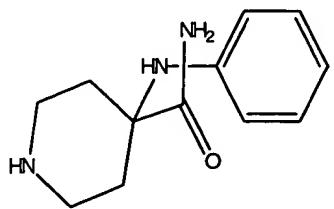
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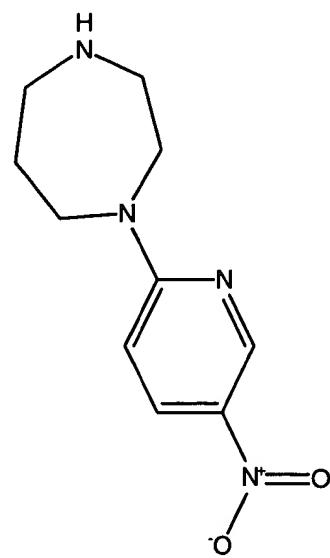
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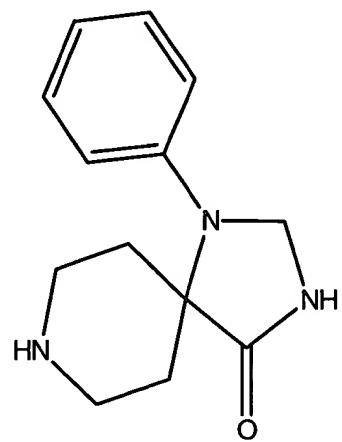
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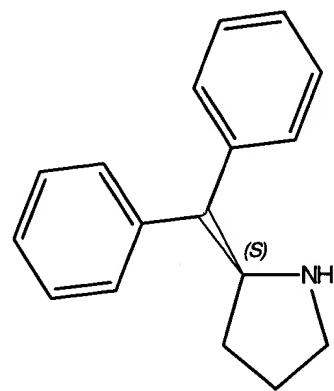
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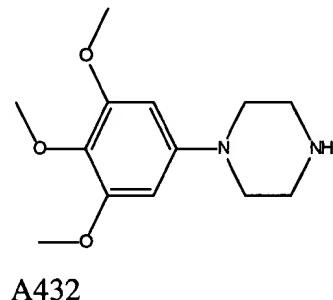
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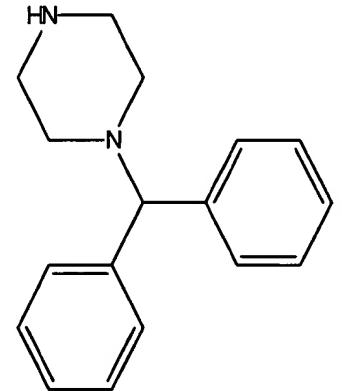
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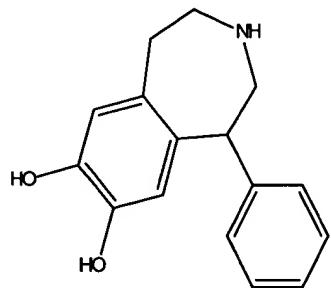
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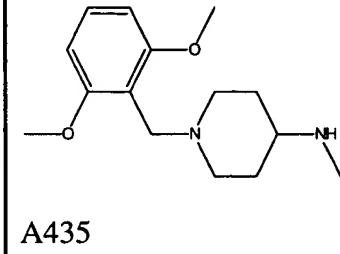
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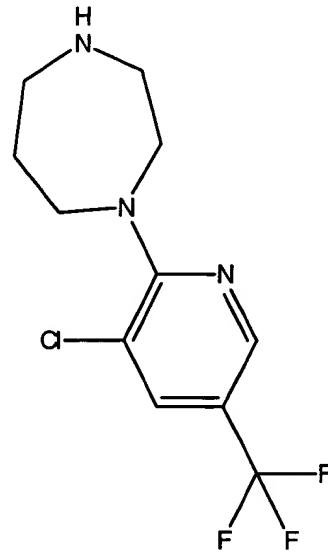
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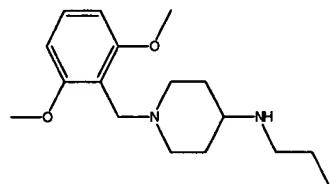
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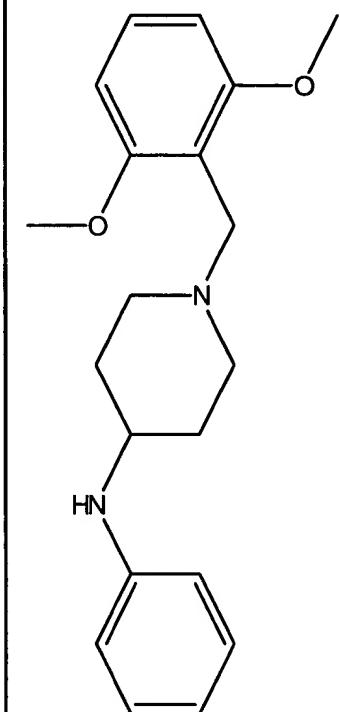
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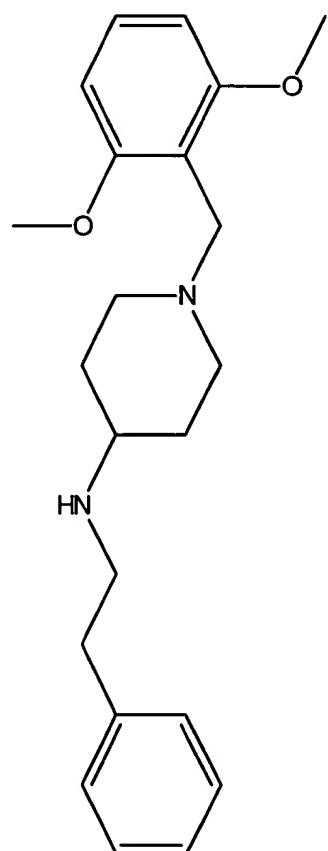
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A437

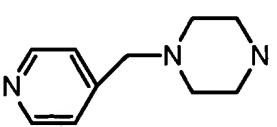
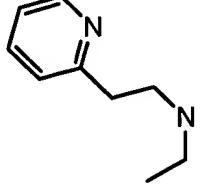
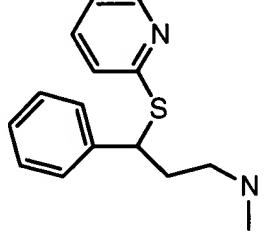
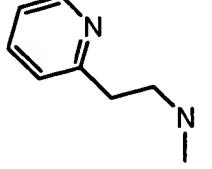
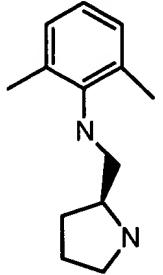
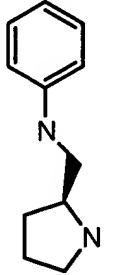
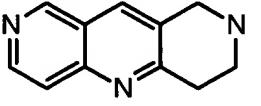
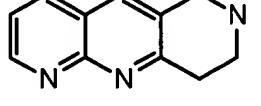
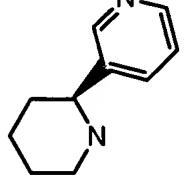


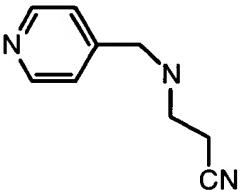
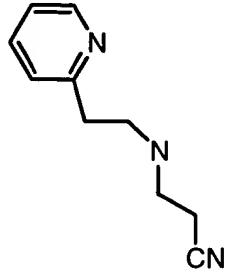
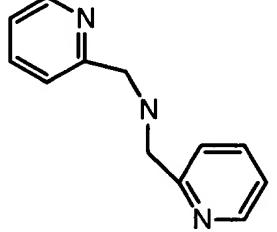
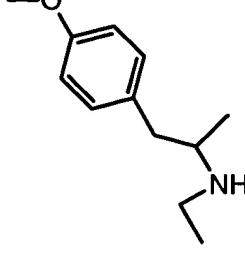
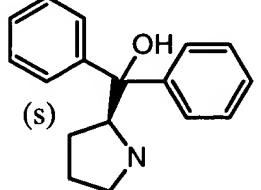
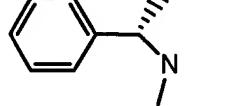
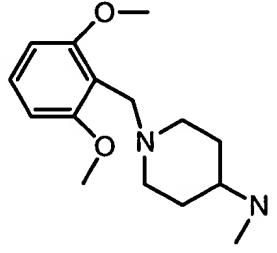
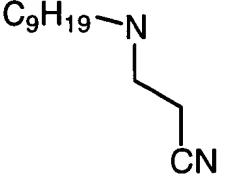
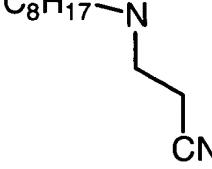
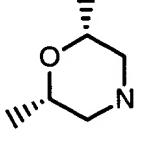
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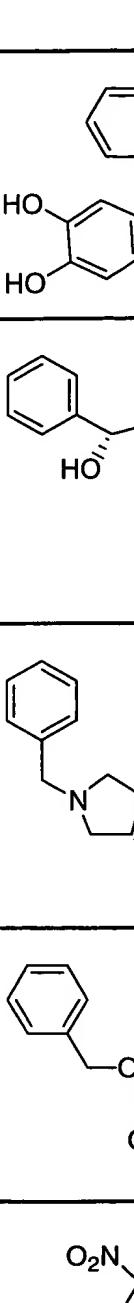
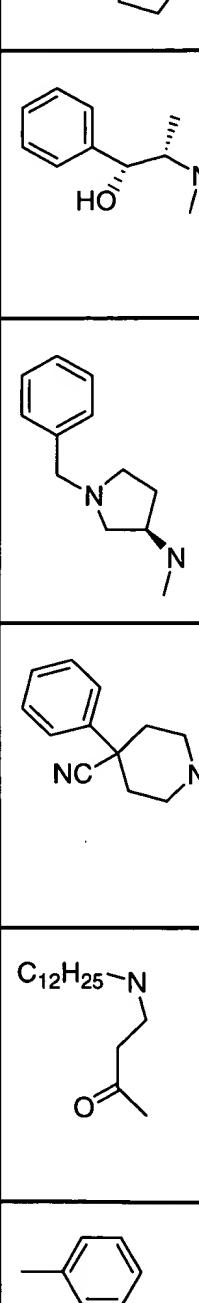
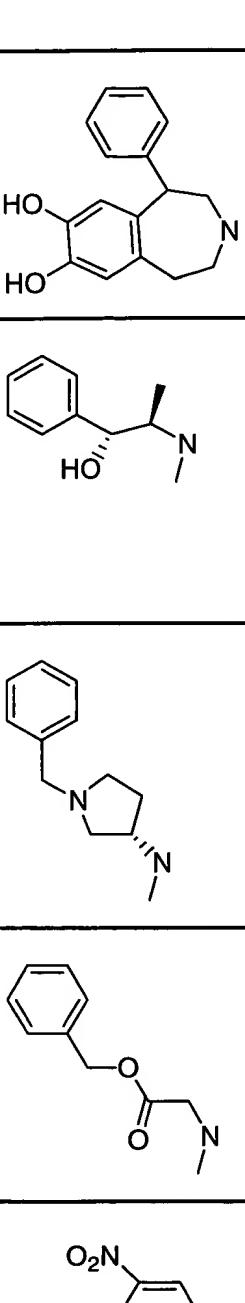
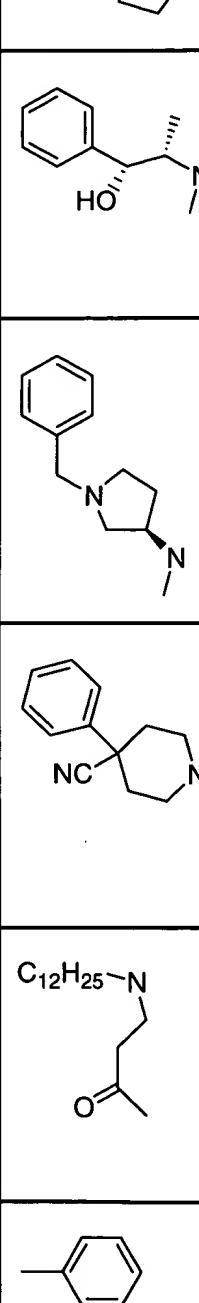
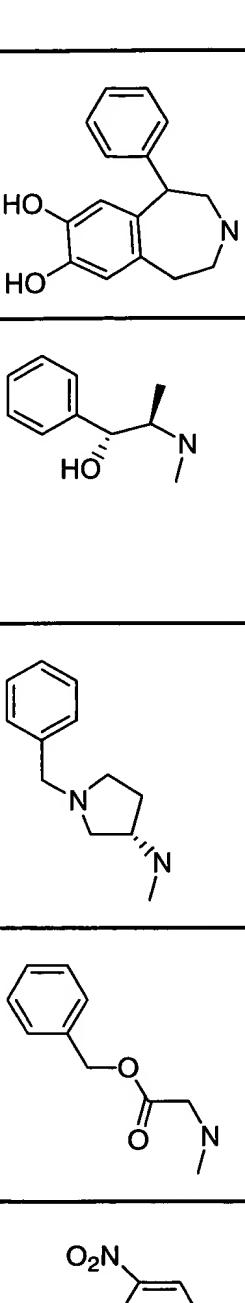
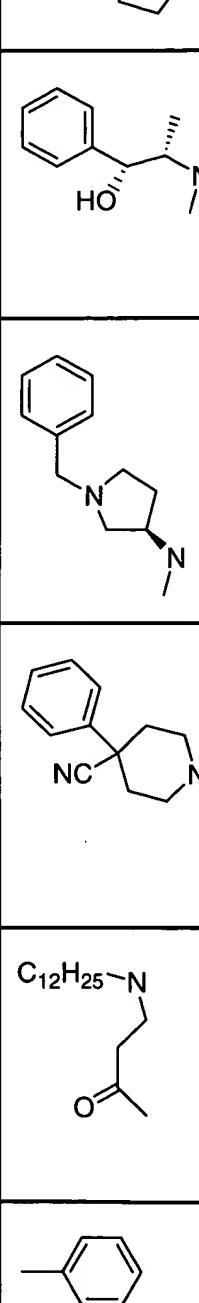
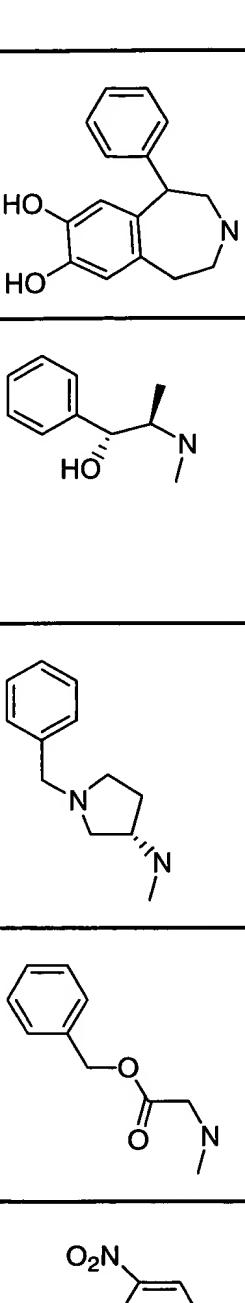
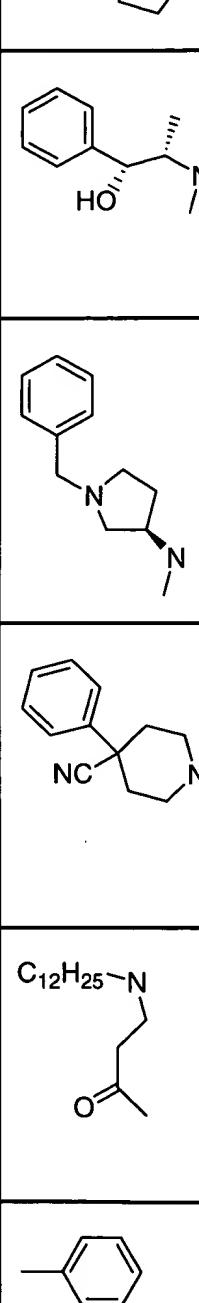
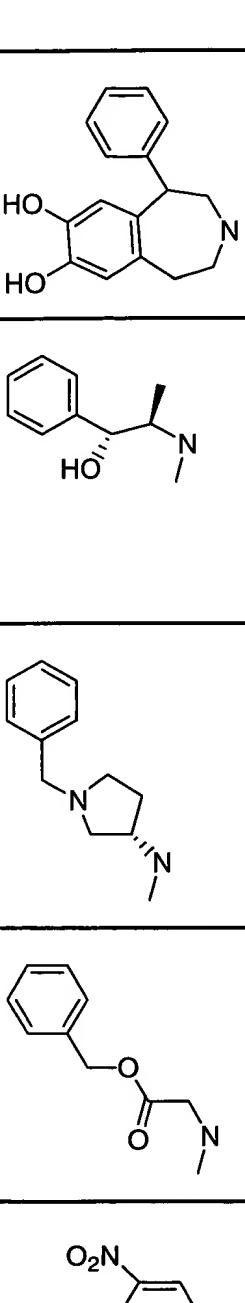
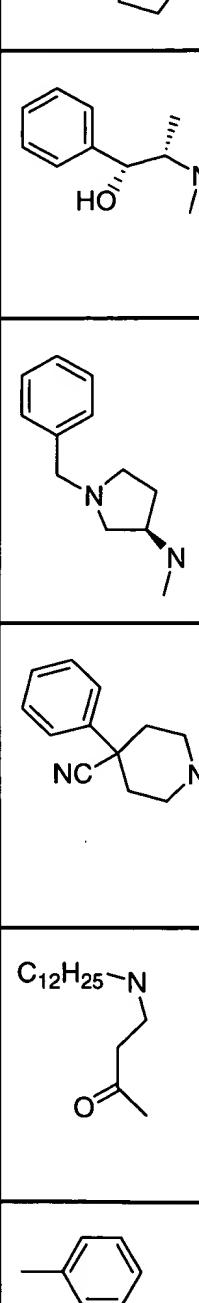
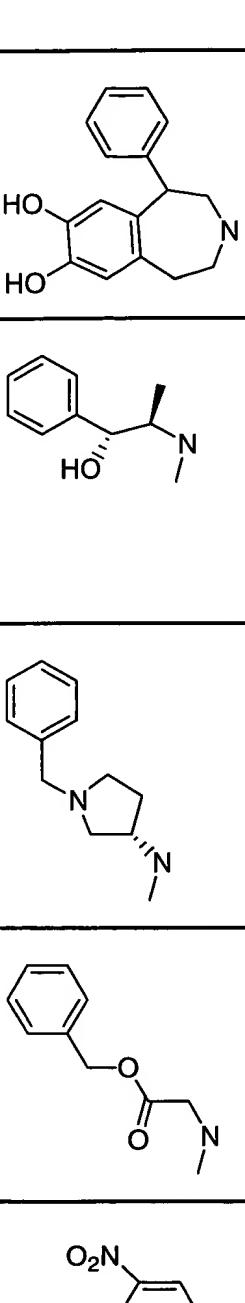
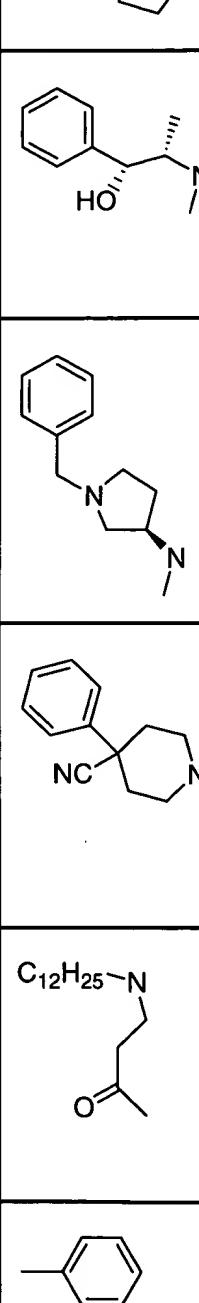
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Preferably, L_2 can also be a group of formula A501-A590 as shown in the following table. L_2 is preferably linked to X through a non-aromatic nitrogen atom (e.g. a secondary amino nitrogen) of L_2 .

5	No.	L_2	No.	L_2	
	A501			A502	
	A503			A504	
	A505			A506	
	A507			A508	
10	A509			A510	

A511		A512	
A513		A514	
A515		A516	
A517		A518	
5		A520	

A521		A522		
A523		A524		
A525		A526		
A527		A528		
5	A529		A530	
	A531		A532	

A533		A534	
A535		A536	
A537		A538	
A539		A540	
A541		A542	
A543		A544	

A545		A546	
A547		A548	
A549		A550	
A551		A552	
5		A553	
A553		A554	
A555		A556	

A569		A570	
A571		A572	
A573		A574	
A575		A576	
A577		A578	
A579		A580	
A581		A582	

A583		A584	
A585		A586	

A587		A588	
A589		A590	

A preferred value for L_2 is A234, A363, A364, A153, A28, A324, A329,
 5 A562, A87, or A239.

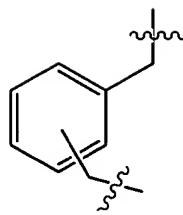
A preferred value for X is alkylene optionally substituted with one, two, or three hydroxy groups, alkylene wherein one, two or three carbon atoms have been replaced by an oxygen atom, -alkylene-phenylene-alkylene- wherein the phenylene ring is optionally substituted with one or two chloro or fluoro groups.

10 Another preferred value for X is an alkylene group having from 3 to 20 carbon atoms; wherein one or more carbon atoms (e.g. 1, 2, 3, or 4) in the alkylene group is optionally replaced with -O-; and wherein the chain is optionally substituted on carbon with one or more (e.g. 1, 2, 3, or 4) hydroxyl.

Another preferred value for X is an alkylene group having from 6 to 15
 15 carbons atoms; wherein one or more carbon atoms (e.g. 1, 2, 3, 4) in the alkylene group is optionally replaced with -O-; and wherein the chain is optionally substituted on carbon with one or more (e.g. 1, 2, 3, or 4) hydroxyl.

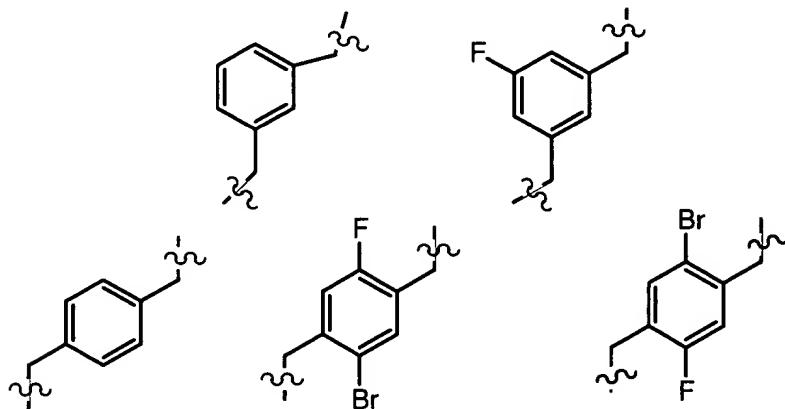
Another preferred value for X is is nonane-1,9-diyl, octane-1,8-diyl,
 propane-1,3-diyl, 2-hydroxypropane-1,3-diyl, or 5-oxa-nonane-1,9-diyl.

20 Another preferred value for X is a group of the following formula:



wherein the phenyl ring is optionally substituted with 1, 2, or 3 fluoro groups.

Another preferred value for X is a group of one of the following formulae:



A preferred group of compounds of formula (I) are compounds wherein R² 5 is selected from formula (i) and (iii); and wherein K" is a bond or methylene.

A preferred group of compounds of formula (I) are compounds wherein R² is formula (i); R³ is hydrogen, methyl, ethyl, propyl, isopropyl, fluoro, or trifluoromethyl; and K" is a bond or methylene.

A preferred group of compounds of formula (I) are compounds wherein R² 10 is formula (iii); R⁶, R⁷, and R⁸ are each hydrogen, methyl, ethyl, propyl, isopropyl, fluoro, or trifluoromethyl; and K" is a bond or methylene.

A preferred group of compounds are compounds of formula (I) wherein R⁴⁶ 15 is alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, or heterocycle; R⁴⁷ is alkyl, substituted alkyl, aryl, acyl, heterocycle, or -COOR⁵⁰ where R⁵⁰ is alkyl; or R⁴⁶ and R⁴⁷ together with the nitrogen atom to which they are attached form heterocycle.

A preferred group of compounds are compounds of formula (I) wherein L_2 is a group of formula (d) wherein R^{46} and R^{47} together with the nitrogen atom to which they are attached form heterocycle which is substituted with 1 to 5 substituents independently selected from the group consisting of alkoxy, substituted

5 alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic,

10 heterocyclooxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-aryl -SO₂-heteroaryl, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, and substituted alkynyl.

A more preferred group of compounds are compounds of formula (I) wherein L_2 is a group of formula (d) wherein R^{46} and R^{47} together with the nitrogen atom to which they are attached form heterocycle which is substituted with 1 to 3 substituents independently selected from the group consisting of alkoxy, substituted

15 alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, hydroxyamino, alkoxyamino, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, and substituted alkynyl.

A preferred group of compounds are compounds of formula (I) wherein L_2 is a group of formula (d) wherein R^{46} and R^{47} together with the nitrogen atom to which they are attached form heterocycle which is substituted with 1 to 5 substituents independently selected from the group consisting of substituted alkyl, alkenyl, substituted alkenyl, alkynyl, and substituted alkynyl.

A preferred group of compounds are compounds of formula (I) wherein L_2 is a group of formula (d) wherein at least one of R^{46} and R^{47} individually, or R^{46} and R^{47} taken together, is a group that comprises a basic nitrogen atom (e.g. a nitrogen

atom with a pKa of preferably at least about 5, more preferably at least about 6, or most preferably at least about 7).

A preferred group of compounds are compounds of formula (I) wherein L₂ is a group of formula (d) wherein R⁴⁶ is a heterocycle, optionally substituted with 1 to 5 substituents independently selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, and substituted alkynyl; and R⁴⁷ is alkyl, substituted alkyl, acyl, or -COOR⁵⁰.

A preferred group of compounds are compounds of formula (I) wherein L₂ is a group of formula (d) wherein R⁴⁶ is alkyl that is substituted by a group that 10 comprises a basic nitrogen atom (e.g. a nitrogen atom with a pKa of preferably at least about 5, more preferably at least about 6, or most preferably at least about 7).

A preferred group of compounds are compounds of formula (I) wherein L₂ is a group of formula (d) wherein R⁴⁶ is alkyl that is optionally substituted with from 1 to 5 substituents independently selected from the group 15 consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, aminoacyl, aminoacyloxy, oxyaminoacyl, cyano, halogen, hydroxyl, keto, thioketo, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, 20 NR^aR^b, wherein R^a and R^b may be the same or different and are chosen from hydrogen, alkyl, substituted alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, and heterocyclic.

A preferred group of compounds are compounds of formula (I) wherein L₂ is a group of formula (d) wherein R⁴⁶ is a heterocycle which is optionally 25 substituted with 1 to 5 substituents independently selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, 30 thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy,

heteraryl, heteroaryloxy, heterocyclic, heterocycloxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteraryl, -SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-aryl -SO₂-heteraryl, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, and substituted alkynyl.

5 A preferred group of compounds are compounds of formula (I) wherein L₂ is a group of formula (d) wherein R⁴⁶ is 3-piperidinyl, 4-piperidinyl, or 3-pyrrolidinyl, which R⁴⁶ is optionally substituted with 1 to 3 substituents independently selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, cyano, halogen, hydroxyl, keto, thioketo, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocycloxy, thiol, thioalkoxy, substituted thioalkoxy, heterocyclic, heterocycloxy, hydroxyamino, alkoxyamino, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, and substituted alkynyl.

10 acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, cyano, halogen, hydroxyl, keto, thioketo, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocycloxy, thiol, thioalkoxy, substituted thioalkoxy, heterocyclic, heterocycloxy, hydroxyamino, alkoxyamino, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, and substituted alkynyl.

15 A preferred group of compounds are compounds of formula (I) wherein R⁴⁶ and R⁴⁷ together with the nitrogen atom to which they are attached form a piperidine or pyrrolidine ring which ring is optionally substituted with 1 to 3 substituents independently selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, cyano, halogen, hydroxyl, keto, thioketo, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocycloxy, thiol, thioalkoxy, substituted thioalkoxy, heterocyclic, heterocycloxy, hydroxyamino, alkoxyamino, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, and substituted alkynyl.

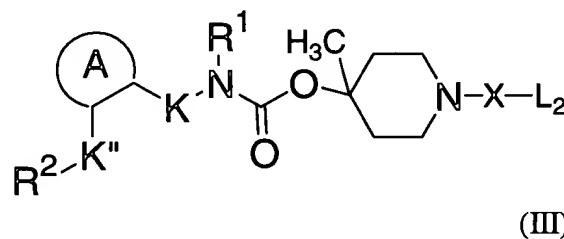
20 acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, cyano, halogen, hydroxyl, keto, thioketo, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocycloxy, thiol, thioalkoxy, substituted thioalkoxy, heterocyclic, heterocycloxy, hydroxyamino, alkoxyamino, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, and substituted alkynyl.

25 A preferred group of compounds are compounds of formula (I) wherein R⁴⁶ and R⁴⁷ together with the nitrogen atom to which they are attached form a heterocycle that is an aza-crown ether (e.g. 1-aza-12-crown-4, 1-aza-15-crown-5, or 1-aza-18-crown-6).

A preferred group of compounds of formula (I) are compounds wherein: A is an aryl or a heteroaryl ring; B" is -O-; R¹ is hydrogen or alkyl; R² is selected from a group consisting of formula (i), (ii), (iii), or "Het":

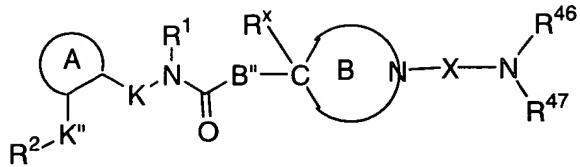
wherein: ----- is an optional double bond; n₁ is an integer of from 1 to 4; n₂ is an integer of from 1 to 3; V is -CH-, -O-, -S(O)n₃- (where n₃ is an integer of from 0 to 2), or -NR⁴- (wherein R⁴ is hydrogen, alkyl, substituted alkyl, aryl, or heteroaryl); "Het" is a heteroaryl ring which optionally attaches the ligand to a linker; R³ is hydrogen, alkyl, amino, substituted amino, -OR^a (where R^a is hydrogen, alkyl, or acyl), or a covalent bond attaching the ligand to a linker; R⁵ is hydrogen, alkyl, amino, substituted amino, -OR^b (where R^b is hydrogen or alkyl), aryl, aralkyl, heteroaralkyl, or a covalent bond attaching the ligand to a linker; R⁶, R⁷, and R⁸ are, independently of each other, hydrogen, halo, hydroxy, alkoxy, haloalkoxy, carboxy, alkoxycarbonyl, alkyl optionally substituted with one, two or three substituents selected from halo, hydroxy, carboxy, alkoxycarbonyl, alkylthio, alkylsulfonyl, amino, substituted amino, or a covalent bond attaching the ligand to a linker; K is a bond or an alkylene group; K" is a bond, -C(O)-, -S(O)n₄- (where n₄ is an integer of from 0 to 2), or an alkylene group optionally substituted with a hydroxyl group; and B is a heterocycloamino group which optionally attaches the ligand to a linker; provided that at least one of the R⁵, R⁶, R⁷, R⁸, "Het", or the heterocycloamino group attaches the ligand to a linker.

A preferred compound of formula (I) is a compound of formula (III):



wherein R², K", A, K, R¹, X, and L₂ have the values defined herein

Another preferred compound of formula (I) is a compound of Formula (Ia):



5

wherein A, R¹, R², R^x, K, K'', B, X, R⁴⁶ and R⁴⁷ are as defined hereinabove.

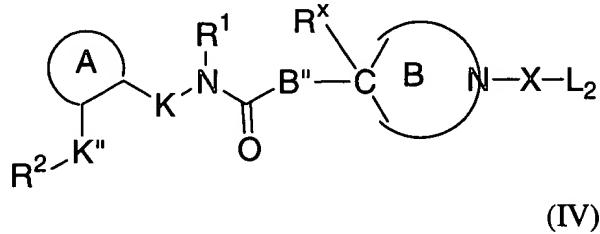
For a compound of Formula (Ia) a preferred group of compounds is that wherein A is phenyl or pyridine; and K and K'' are bond.

For a compound of Formula (Ia) another preferred group of is that wherein

10 A is phenyl or pyridine; R² is phenyl; and K and K'' are bond.

For a compound of Formula (Ia) another preferred group of compounds is that wherein B has any of the preferred values identified herein.

The invention also provides a compound of formula (IV):



(IV)

15 wherein L₂ is an organic group comprising at least one (e.g. 1, 2, 3, or 4) primary, secondary or tertiary amine; and wherein R², K'', A, K, R¹, R^x, and X have any of the values defined herein; or a pharmaceutically acceptable salt; or prodrug thereof. Typically, the amine of L₂ should be a basic, having a pH of at least about 5, and preferably at least about 6. The nature of the group -X-L₂ is not critical provided

20 the compound (IV) has suitable properties (e.g. solubility, stability, and toxicity) for its intended use (e.g. as a drug or as a pharmacological tool). Typically the group -X-L₂ will have a molecular weight below 500 and preferably below about 300. Additionally, the group -X-L₂ preferably comprises 5 or fewer hydrogen bond donors (e.g. OH, -NHR-, and -C(=O)NHR-) and ten or fewer hydrogen bond acceptors (e.g. -O-, -NRR-, and -S-). Preferably, the piperidine nitrogen shown in

formula (IV) is separated from an amine of the group L₂ by about 15 angstroms to about 75 angstroms (based on conventionally acceptable bond lengths and angles). More preferably, the piperidine nitrogen is separated from an amine of the group L₂ by about 25 angstroms to about 50 angstroms. Preferred compounds of formula 5 (IV) also have a log D between about -3 and about 5. Using the above parameters, one skilled in the art can readily determine compounds of formula (I) possessing the desired properties for an intended use.

GENERAL SYNTHETIC SCHEMES

10 Compounds of this invention can be made by the methods depicted in the reaction schemes shown below.

The starting materials and reagents used in preparing these compounds are either available from commercial suppliers such as Aldrich Chemical Co., (Milwaukee, Wisconsin, USA), Bachem (Torrance, California, USA), 15 Emka-Chemie, or Sigma (St. Louis, Missouri, USA) or are prepared by methods known to those skilled in the art following procedures set forth in references such as Fieser and Fieser's Reagents for Organic Synthesis, Volumes 1-15 (John Wiley and Sons, 1991); Rodd's Chemistry of Carbon Compounds, Volumes 1-5 and Supplements (Elsevier Science Publishers, 1989), Organic Reactions, Volumes 20 1-40 (John Wiley and Sons, 1991), March's Advanced Organic Chemistry, (John Wiley and Sons, 4th Edition), and Larock's Comprehensive Organic Transformations (VCH Publishers Inc., 1989).

The starting materials and the intermediates of the reaction may be isolated and purified if desired using conventional techniques, including but not limited to 25 filtration, distillation, crystallization, chromatography, and the like. Such materials may be characterized using conventional means, including physical constants and spectral data.

Furthermore, it will be appreciated that where typical or preferred process conditions (i.e., reaction temperatures, times, mole ratios of reactants, solvents, 30 pressures, etc.) are given, other process conditions can also be used unless

otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvent used, but such conditions can be determined by one skilled in the art by routine optimization procedures.

Additionally, as will be apparent to those skilled in the art, conventional

5 protecting groups may be necessary to prevent certain functional groups from undergoing undesired reactions. The choice of a suitable protecting group for a particular functional group as well as suitable conditions for protection and deprotection are well known in the art. For example, numerous protecting groups, and their introduction and removal, are described in T. W. Greene and G. M. Wuts,

10 *Protecting Groups in Organic Synthesis*, Second Edition, Wiley, New York, 1991, and references cited therein.

These schemes are merely illustrative of some methods by which the compounds of this invention can be synthesized, and various modifications to these schemes can be made and will be suggested to one skilled in the art having referred

15 to this disclosure.

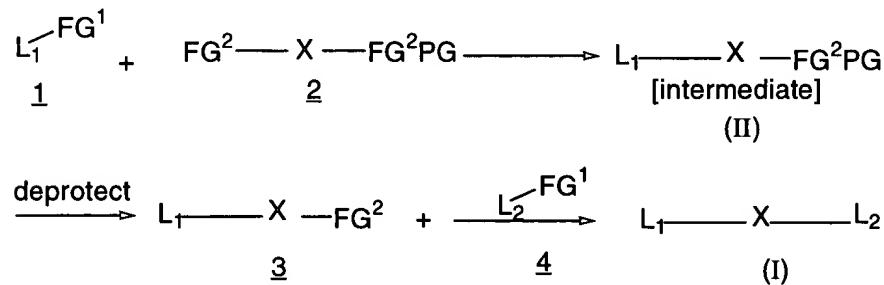
Preparation of a compound of Formula (I)

In general, compounds of Formula (I) can be prepared as illustrated and described in Schemes A.

20

Scheme A

25



A compound of Formula (I) is prepared by covalently attaching one

30 equivalent of a compound of formula 1 with a compound of formula 2 where X is a

linker as defined herein, FG¹ is a functional group, FG² is a functional group that is complimentary to FG¹, PG is a protecting group, and FG²PG is a protected functional group to give an intermediate of formula (II). Deprotection of the functional group on the linker, followed by reaction of resulting compound 3 with 5 one equivalent of compound 4, then provides a compound of Formula (I). The reaction conditions used to link compounds 1 and 4 to compound 2 and 3 depend on the nature of the functional groups on compounds 1, 2, 3 and 4 which in turn depend on the type of linkage desired. Examples of the functional groups and the reaction conditions that can be used to generate a specific linkage is described 10 below.

Table I
Representative Complementary Binding Chemistries

	<u>First Reactive Group</u>	<u>Second Reactive Group</u>	<u>Linkage</u>
15	carboxyl	amine	amide
	sulfonyl	halide	sulfonamide
	hydroxyl	alkyl/aryl halide	ether
	hydroxyl	isocyanate	urethane
	amine	epoxide	β-hydroxyamine
20	amine	alkyl/aryl halide	alkylamine
	hydroxyl	carboxyl	ester

Reaction between a carboxylic acid of either the linker or the ligand and a primary or secondary amine of the ligand or the linker in the presence of suitable, 25 well-known activating agents such as dicyclohexylcarbodiimide, results in formation of an amide bond covalently linking the ligand to the linker; reaction between an amine group of either the linker or the ligand and a sulfonyl halide of the ligand or the linker, in the presence of a base such as triethylamine, pyridine, and the like ,results in formation of a sulfonamide bond covalently linking the 30 ligand to the linker; and reaction between an alcohol or phenol group of either the

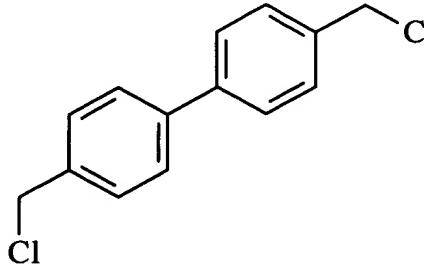
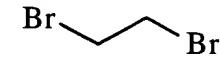
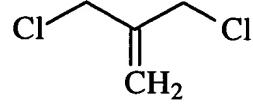
linker or the ligand and an alkyl or aryl halide of the ligand or the linker in the presence of a base such as triethylamine, pyridine, and the like, results in formation of an ether bond covalently linking the ligand to the linker.

Suitable dihydroxyl and dihalo starting materials useful for incorporating a 5 group X into a compound of the invention are shown in the following table.

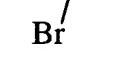
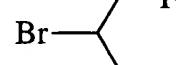
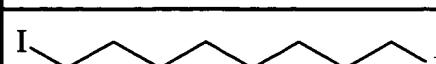
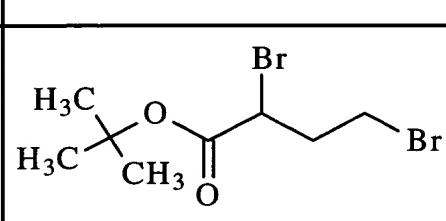
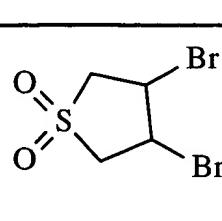
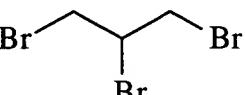
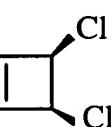
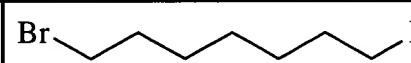
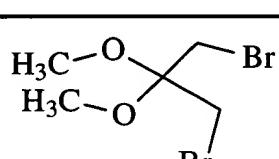
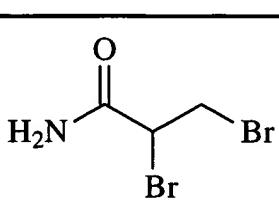
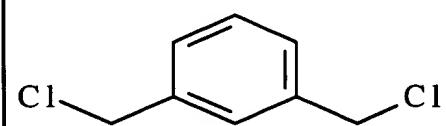
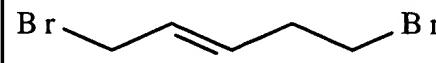
Preferably, an alcohol is reacted with a ligand bearing a leaving group to provide an ether bond, while a dihalo compound is preferably reacted with an amine of the ligand to form a substituted amine.

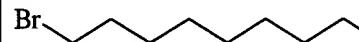
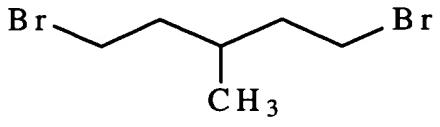
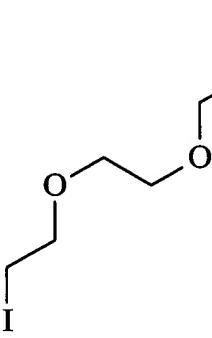
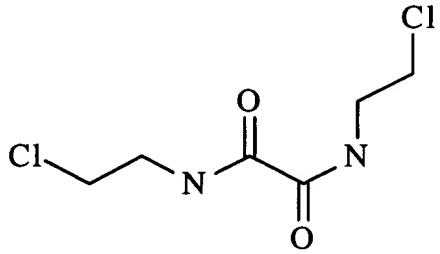
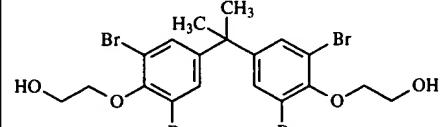
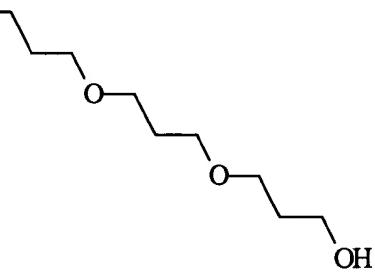
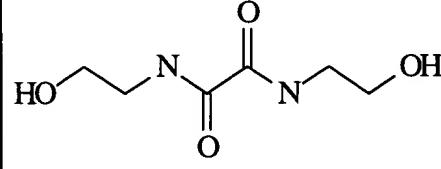
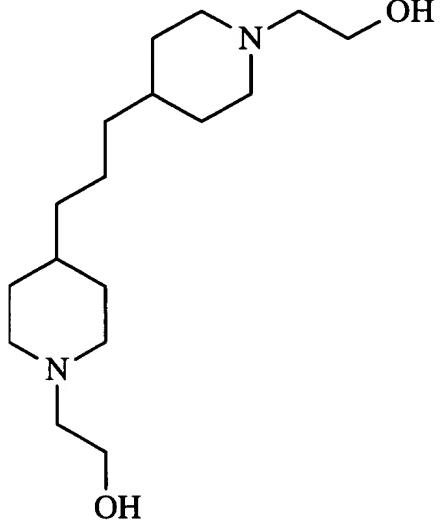
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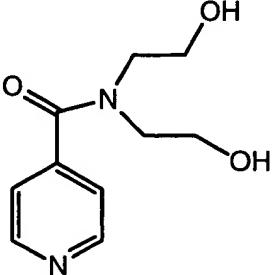
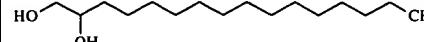
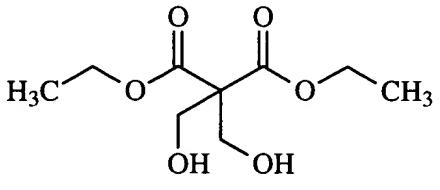
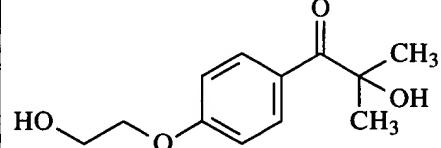
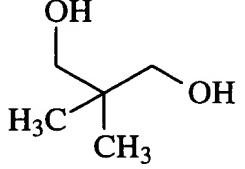
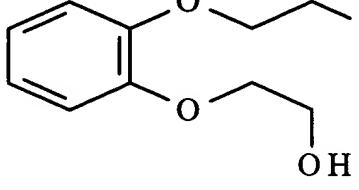
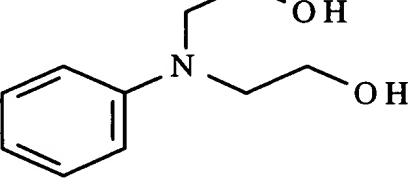
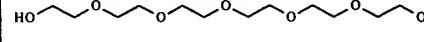
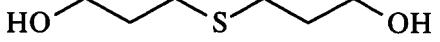
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X3		X4	
X5		X6	
X7		X8	

No.	X	No.	X
X9		X10	
X11		X12	

No.	X	No.	X
X13		X14	
X15		X16	
X17		X18	
X19		X20	
5		X22	

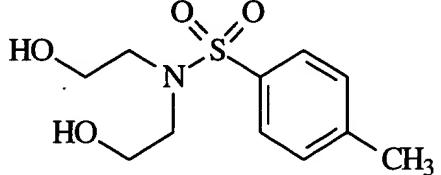
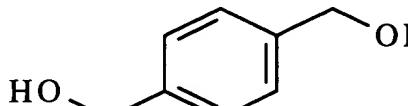
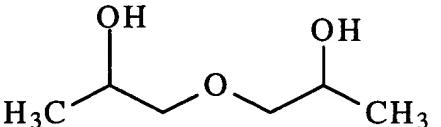
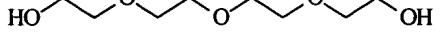
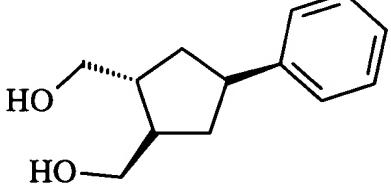
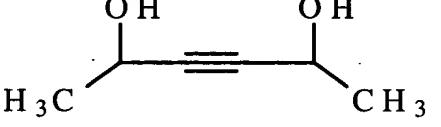
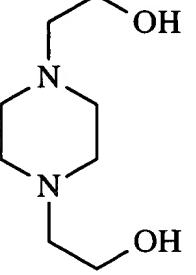
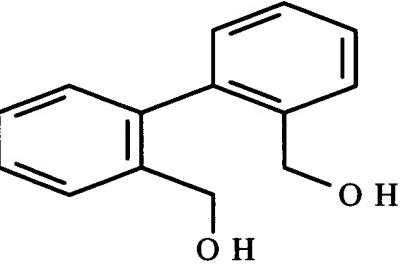
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X25		X26	
X27		X28	
X29		X30	
X31		X32	
X33		X34	
X35		X36	

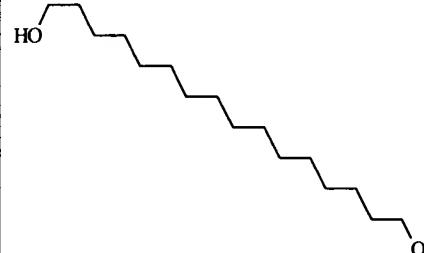
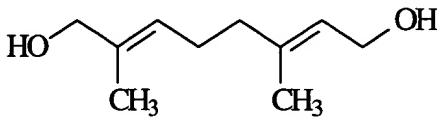
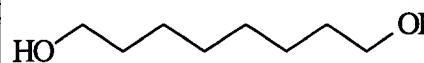
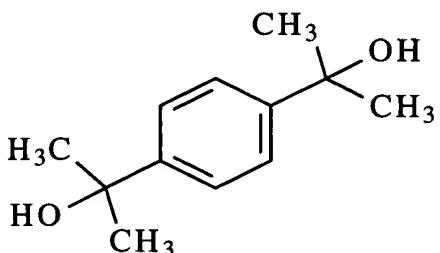
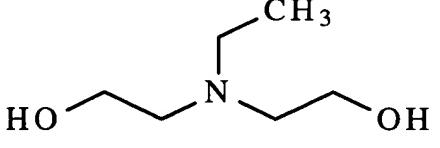
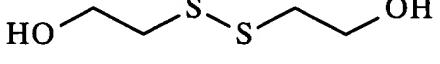
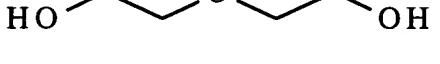
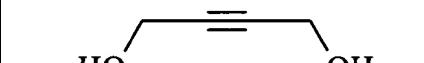
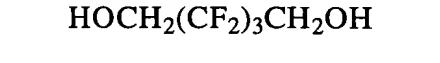
No.	X	No.	X
X37		X38	
X39		X40	
X41		X42	
X43		X44	

No.	X	No.	X
X45		X46	
X47		X48	
X49		X50	
X51		X52	
5		X54	

No.	X	No.	X
X55	$\text{HOCH}_2(\text{CF}_2)_8\text{CH}_2\text{OH}$	X56	
X57		X58	
X59	$\text{HO}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{OH}$	X60	$\text{HO}-\text{CH}_2-\text{CH}_2-\text{S}-\text{CH}_2-\text{CH}_2-\text{S}-\text{CH}_2-\text{CH}_2-\text{OH}$
X61		X62	
5		X64	$\text{HO}-\text{CH}_2-\text{CH}_2-\text{OH}$
X63		X65	
X65	$\text{HO}-\text{CH}_2-\text{O}-\text{CH}_2-\text{O}-\text{CH}_2-\text{O}-\text{CH}_2-\text{O}-\text{CH}_2-\text{O}-\text{CH}_2-\text{OH}$	X66	

No.	X	No.	X
X67	<chem>CCCCCCCCCO</chem>	X68	<chem>OCC(O)c1ccc(O)cc1</chem>
X69	<chem>HOCH2CH2CH2CH2OH</chem>	X70	<chem>OCC(O)c1ccnc(CO)c1</chem>
X71	<chem>OCC(O)c1ccc2c(c1)ccc3c2ccc(O)cc3</chem>	X72	<chem>CCCCCCCCO</chem>
X73	<chem>CCCCCCCCO</chem>	X74	<chem>CCCCCCCC(O)C(C)O</chem>
5			
X75	<chem>CC1(C)CC(O)CC2(C)CC(O)CC12</chem>	X76	<chem>OCC1CCCCC1O</chem>
X77	<chem>CCCCCCCCCCCCO</chem>	X78	<chem>OCC(O)CCCCCCCC=CH2</chem>

No.	X	No.	X
X79		X80	
X81		X82	
X83		X84	
X85		X86	
5		X88	

No.	X	No.	X
X89		X90	
X91		X92	
X93		X94	
X95		X96	
5			
X97		X98	
X99		X100	

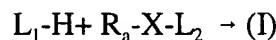
Typically, a compound selected for use as a ligand will have at least one functional group, such as an amino, hydroxyl, thiol or carboxyl group and the like, which allows the compound to be readily coupled to the linker. Compounds having

such functionality are either known in the art or can be prepared by routine modification of known compounds using conventional reagents and procedures.

A compound of formula (a) wherein A is phenyl, pyridyl, and the like can be prepared as described in EP 747 355 and as described by Naito, R. et al., *Chem.*

5 *Pharm. Bull.*, 1998, 46(8), 1286.

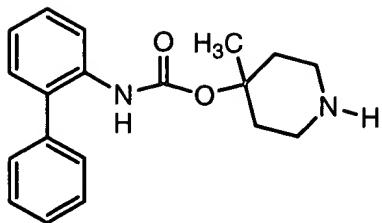
Scheme B



10 A compound of formula (I) wherein L_1 comprises a nitrogen that is bonded to X, can be prepared by alkylating a corresponding compound of formula $L_1\text{-H}$ wherein -H is bound to the nitrogen, with a corresponding compound of $R_a\text{-X-L}_2$ wherein X and L_2 have any of the values defined herein and R_a is a suitable leaving group. Suitable leaving groups and conditions for the alkylation of an amine are
15 known in the art (for example, see *Advanced Organic Chemistry, Reaction Mechanisms and Structure*, 4 ed., 1992, Jerry March, John Wiley & Sons, New York. For example, R_a can be halo (e.g. chloro, bromo, or iodo), methylsulfonyl, 4-tolylsulfonyl, mesyl, or trifluoromethylsulfonyl.

Accordingly, the invention provides a method for preparing a compound of
20 formula (I) wherein L_1 comprises a nitrogen that is bonded to X, comprising alkylating a corresponding compound of formula $L_1\text{-H}$ with a compound of $R_a\text{-X-L}_2$ wherein X and L_2 have any of the values defined herein and R_a is a suitable leaving group.

The invention also provides a compound of formula $L_1\text{-H}$ wherein L_1 has
25 any of the values defined herein. The following compound is a preferred compound of formula $L_1\text{-H}$:

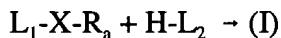


The compound of formula $L_1\text{-H}$ can also be alkylated by treatment with an aldehyde of formula $L_2\text{-V-CHO}$ (wherein $-\text{V-CH}_2\text{-}$ is equivalent to $-\text{X-}$), under reductive alkylation conditions. Reagents and conditions suitable for carrying out the reductive alkylation of an amine are known in the art (for example, see

5 Advanced Organic Chemistry, Reaction Mechanisms and Structure, 4 ed., 1992, Jerry March, John Wiley & Sons, New York).

Accordingly, the invention provides a method for preparing a compound of formula (I) wherein L_1 comprises a nitrogen that is bonded to X , comprising alkylating a corresponding compound of formula $L_1\text{-H}$ with a compound of formula 10 $L_2\text{-V-CHO}$ (wherein $-\text{V-CH}_2\text{-}$ has any of the values for $-\text{X-}$ described herein).

Scheme C



15

A compound of formula (I) wherein L_2 comprises a nitrogen that is bonded to X , can be prepared by alkylating a corresponding compound of formula $L_2\text{-H}$ wherein $-\text{H}$ is bound to the nitrogen, with a corresponding compound of $L_1\text{-X-}R_a$ wherein X and L_1 have any of the values defined herein and R_a is a suitable leaving 20 group. Suitable leaving groups and conditions for the alkylation of an amine are known in the art (for example, see Advanced Organic Chemistry, Reaction Mechanisms and Structure, 4 ed., 1992, Jerry March, John Wiley & Sons, New York. For example, R_a can be halo (e.g. chloro, bromo, or iodo), methylsulfonyl, 4-tolylsulfonyl, mesyl, or trifluoromethylsulfonyl.

Accordingly, the invention provides a method for preparing a compound of formula (I) wherein L_2 comprises a nitrogen that is bonded to X, comprising alkylating a corresponding compound of formula L_2 -H with a compound of L_1 -X- R_a wherein X and L_1 have any of the values defined herein and R_a is a suitable leaving group.

The compound of formula L_2 -H can also be alkylated by treatment with an aldehyde of formula L_1 -V-CHO (wherein -V-CH₂- is equivalent to -X-), under reductive alkylation conditions. Reagents and conditions suitable for carrying out the reductive alkylation of an amine are known in the art (for example, see

10 Advanced Organic Chemistry, Reaction Mechanisms and Structure, 4 ed., 1992, Jerry March, John Wiley & Sons, New York).

Accordingly, the invention provides a method for preparing a compound of formula (I) wherein L_2 comprises a nitrogen that is bonded to X, comprising alkylating a corresponding compound of formula L_2 -H with a compound of formula $15 L_1$ -V-CHO (wherein -V-CH₂- has any of the values for -X- described herein).

It will be understood that the alkylation reactions in Schemes B and C can optionally be carried out using suitably protected derivatives of L_1 -H, L_2 -H, L_1 -X- R_a , R_a -X- L_2 , L_1 -V-CHO, and L_2 -V-CHO. Suitable protecting groups as well as conditions for their incorporation and removal are known in the art (for example, 20 see Greene, T.W.; Wutz, P.G.M. "Protecting Groups In Organic Synthesis" second edition, 1991, New York, John Wiley & sons, Inc.). Thus, a compound of formula (I) can also be prepared by deprotecting a corresponding compound of formula (I) bearing one or more protecting groups.

Accordingly, the invention provides a method for preparing a compound of 25 formula (I) comprising deprotecting a corresponding compound of formula (I) that bears one or more protecting groups. The invention also provides an intermediate compound of formula (I) that bears one or more protecting groups.

Combinatorial Synthesis

30 Compounds of formula (I) can conveniently be prepared using combinatorial synthesis methods (e.g. solid phase and solution phase combinatorial

synthesis methods) that are known in the art. For example, compounds of formula (I) can be prepared using combinatorial methods like those described in International Patent Application Publication Number WO 99/64043.

5

Utility, Testing, and Administration

Utility

The compounds of this invention are muscarinic receptor antagonists or agonists. A preferred sub-group are M₂ muscarinic receptor antagonists.

10 Accordingly, the compounds and pharmaceutical compositions of this invention are useful in the treatment and prevention of diseases mediated by these receptors such as chronic obstructive pulmonary disease, asthma, irritable bowel syndrome, urinary incontinence, rhinitis, spasmodic colitis, chronic cystitis, and Alzheimer's disease, senile dementia, glaucoma, schizophrenia, gastroesophageal reflux disease, 15 cardiac arrhythmia, hyper salvation syndromes, and the like.

Testing

The ability of the compounds of formula (I) to inhibit a muscarinic receptor (e.g. the M₂ or M₃ subtype) may be demonstrated using a variety of *in vitro* assays 20 and *in vivo* assays known in the field, or may be demonstrated using an assay described in biological examples 1-6 below.

Pharmaceutical Formulations

When employed as pharmaceuticals, the compounds of this invention are 25 usually administered in the form of pharmaceutical compositions. These compounds can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intravenous, intramuscular, intravesicular, and intranasal. These compounds are effective as both injectable and oral compositions. Such compositions are prepared in a manner well known in the 30 pharmaceutical art and comprise at least one active compound.

This invention also includes pharmaceutical compositions which contain, as the active ingredient, one or more of the compounds described herein associated with pharmaceutically acceptable carriers. In making the compositions of this invention, the active ingredient is usually mixed with an excipient, diluted by an

5 excipient or enclosed within such a carrier which can be in the form of a capsule, sachet, paper or other container. When the excipient serves as a diluent, it can be a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions,

10 syrups, aerosols (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders.

In preparing a formulation, it may be necessary to mill the active compound to provide the appropriate particle size prior to combining with the other

15 ingredients. If the active compound is substantially insoluble, it ordinarily is milled to a particle size of less than 200 mesh. If the active compound is substantially water soluble, the particle size is normally adjusted by milling to provide a substantially uniform distribution in the formulation, e.g. about 40 mesh.

Some examples of suitable excipients include lactose, dextrose, sucrose,

20 sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, sterile water, syrup, and methyl cellulose. The formulations can additionally include: lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as

25 methyl- and propylhydroxy-benzoates; sweetening agents; and flavoring agents. The compositions of the invention can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures known in the art.

The compositions are preferably formulated in a unit dosage form, each

30 dosage containing from about 0.001 to about 1 g, usually about 0.1 to 500 mg, more usually about 1 to about 30 mg, of the active ingredient. The term "unit dosage

forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient. Preferably, the compound of Formula (I) 5 above is employed at no more than about 20 weight percent of the pharmaceutical composition, more preferably no more than about 15 weight percent, with the balance being pharmaceutically inert carrier(s).

The active compound is effective over a wide dosage range and is generally administered in a pharmaceutically effective amount. It, will be understood, 10 however, that the amount of the compound actually administered will be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered and its relative activity, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

15 For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical excipient to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition 20 so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation is then subdivided into unit dosage forms of the type described above containing from, for example, 0.1 to about 500 mg of the active ingredient of the present invention.

The tablets or pills of the present invention may be coated or otherwise 25 compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permit the inner component to pass intact into the 30 duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and

mixtures of polymeric acids with such materials as shellac, cetyl alcohol, and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous 5 solutions, suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils such as corn oil, cottonseed oil, sesame oil, coconut oil, or peanut oil, as well as elixirs and similar pharmaceutical vehicles.

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or 10 mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as described *supra*. Preferably the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in preferably pharmaceutically acceptable solvents may be nebulized by use of inert gases. Nebulized solutions may be inhaled 15 directly from the nebulizing device or the nebulizing device may be attached to a face mask tent, or intermittent positive pressure breathing machine. Solution, suspension, or powder compositions may be administered, preferably orally or nasally, from devices which deliver the formulation in an appropriate manner.

20 **EXAMPLES**

The following preparations and examples are given to enable those skilled in the art to more clearly understand and to practice the present invention. They should not be considered as limiting the scope of the invention, but merely as being illustrative and representative thereof.

25 In the examples below, the following abbreviations have the following meanings. Unless otherwise stated, all temperatures are in degrees Celsius. If an abbreviation is not defined, it has its generally accepted meaning.

30	g	=	gram
	mg	=	milligram
	min	=	minute
	ml	=	milliliter

mmol = millimol

5

Synthetic Examples

Example 1

Synthesis of 4-methylpiperidin-4-yl-*N*-(2-biphenyl)carbamate

10 Step 1

N-benzyl-4-piperidone (2 g, 10.6 mmol) was dissolved in anhydrous tetrahydrofuran (20 ml) and the solution was degassed. After cooling the reaction mixture to -78 °C, a solution of methylmagnesium bromide (7 ml of 3M solution in tetrahydrofuran, 21.2 mmol) was added via syringe over 5 min. The reaction 15 mixture was allowed to warm to 0 °C and then stirred for 2 h. Ammonium chloride (60 ml, 0.2M) was added slowly to quench the reaction. The solution was basified to pH 12 and then extracted with chloroform. The organic layer was washed with brine, dried over magnesium sulfate and concentrated to provide *N*-benzyl-4-hydroxy-4-methylpiperidine in quantitative yield.

20 Step 2

N-benzyl-4-hydroxy-4-methylpiperidine (7.14 g, 34.8 mmol) was combined with biphenyl-2-isocyanate into a 40 ml high pressure tube without solvent. The tube was capped and a blast shield was placed. The reaction mixture was heated with stirring in an oil bath to 70 oC for 12 h. Ethyl acetate was added after cooling 25 and the organic layer was washed with saturated bicarbonate, brine and then dried over magnesium sulfate. The solvent was removed under vacuum to provide 4-hydroxy-4-methylpiperidine (10 g, 36%).

Step 3

4-Hydroxy-4-methylpiperidine (0.2 g, 0.5 mmol) was dissolved in anhydrous methanol (5 ml) and nitrogen gas was vigorously bubbled through the solution for 30 10 min. Palladium hydroxide (Pearlman's catalyst, 50 mg) and hydrochloric acid (50 ul, 37%) was added under a stream of nitrogen. A balloon containing hydrogen

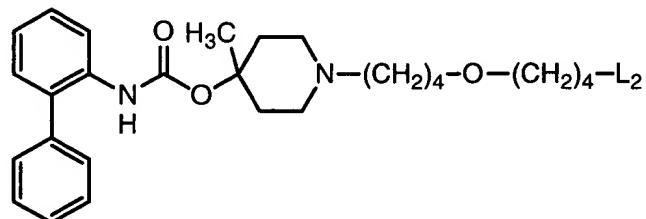
gas was placed and the solution was allowed to stir for 12 h. The solution was concentrated under vacuum and then partitioned between ethyl acetate and 0.1 N hydrochloric acid. The aqueous layer was extracted with ethyl acetate. The organic layers were combined, dried over MgSO_4 , and concentrated to provide 4-

5 methylpiperidin-4-yl-*N*-(2-biphenylyl)carbamate in quantitative yield.

Following the procedures described above but substituting appropriate starting materials, the compounds of the invention (formula (VI)) listed in Table A below were prepared. In the following Tables A and B, L_2 is linked to X through the secondary non-aromatic amine of L_2 unless otherwise noted.

10

Table A



(VI)

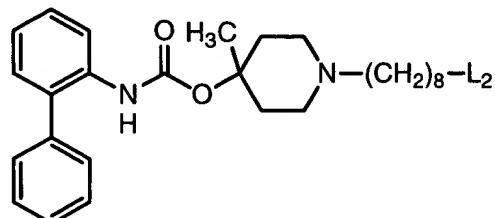
Compound	L_2	Mass Spec Found
1	A501	614.8
2	A502	587.8
15	A503	696.0
4	A504	573.8
5	A397	619.7
6	A337	565.8
7	A303	524.7
20	A505	641.9
8	A506	613.9
9	A431	674.9
10	A388	612.9
11		

12	A366	598.8	
13	A523	593.8	
14	A417	637.9	
15	A357	590.8	
5	16	A319	551.7
17	A381	608.8	
18	A351	579.8	
19	A338	565.8	
10	20	A362	594.8
21	A507	508.7	
22	A329	552.8	
23	A402	623.8	
24	A403	623.8	
25	A315	550.8	
15	26	A333	564.8

Following the procedures described above but substituting appropriate starting materials, the compounds of the invention (formula (VII)) listed in Table B below were prepared.

20

Table B



(VII)

Compound	L2	Mass Spec Found
27	A508	606.8

	28	A509	606.8
	29	A501	598.8
	30	A510	583.6
	31	A502	571.8
5	32	A43	620.9
	33	A511	582.8
	34	A512	596.8
	35	A513	620.9
	36	A503	680.0
10	37	A504	557.8
	38	A514	614.9
	39	A141	676.9
	40	A169	586.8
	41	A164	586.8
15	42	A199	536.8
	43	A70	611.9
	44	A73	611.9
	45	A156	674.9
	46	A230	606.9
20	47	A8	600.9
	48	A515	674.9
	49	A516	556.8
	50	A97	580.8
	51	A96	554.8
25	52	A190	574.9
	53	A517	686.0
	54	A62	611.9
	55	A74	585.8

	56	A65	585.8
	57	A193	617.9
	58	A142	673.9
	59	A177	625.9
5	60	A68	584.8
	61	398	605.8
	62	A166	611.9
	63	A80	589.9
	64	332	538.8
10	65	A34	535.7
	66	A93	549.8
	67	A163	535.8
	68	A59	563.8
	69	A49	652.9
15	70	A31	583.8
	71	A205	565.8
	72	A154	581.9
	73	A229	616.9
	74	A43	621.9
20	75	A94	582.8
	76	A511 [#]	583.8
	77	A218	587.8
	78	A123	563.8
	79	A518	617.9
25	80	A519	603.9
	81	A17	596.9
	82	A21	602.8
	83	A25	638.9

	84	A33	621.9
	85	420	623.9
	86	A135	610.9
	87	A210	612.9
5	88	A88	600.9
	89	A72	598.8
	90	A26	638.9
	91	A75	582.8
	92	A171	622.9
10	93	A81	550.8
	94	412	614.8
	95	421	623.9
	96	A232	586.8
	97	A20	596.8
15	98	A153	640.9
	99	A9	554.8
	100	A520	536.8
	101	A237	618.8
	102	A10	586.8
20	103	A98	607.8
	104	A111	535.7
	105	A4	563.8
	106	A19	522.7
	107	A521	600.9
25	108	A103*	599.9
	109	A103**	600.9
	110	A60	605.9
	111	A522	669.9

	112	A109	584.9
	113	A197	537.8
	114	A235	592.8
	115	A233	601.8
5	116	A195	532.7
	117	A22	595.8
	118	A1	534.8
	119	A63	549.8
	120	A225	577.2
10	121	A77	654.9
	122	A222	588.8
	123	A211	619.9
	124	A115	536.8
	125	A307	520.8
15	126	A397	603.7
	127	A333	549.8
	128	A303	508.7
	129	A505®	625.9
	130	A506®	597.9
20	131	A431	658.9
	132	A388	596.9
	133	A366	582.8
	134	A523	577.8
	135	A417	621.9
25	136	A357	574.8
	137	A319	535.7
	138	A381	592.8
	139	A351	563.8

140	A338	549.8
141	A362	578.8
142	A507	492.7
143	A402	607.8
144	A403	607.8
145	A315	534.8
146	A333	548.8

* X is attached to the pyridyl nitrogen; Attached *X is attached to the secondary amine of A103;

**X is attached to the tertiary amine of A103; [@] X attached at the pyrrolidinyl nitrogen

10

Formulation Examples

Example 1

Hard gelatin capsules containing the following ingredients are prepared:

		Quantity
	Ingredient	(mg/capsule)
15	Active Ingredient	30.0
	Starch	305.0
	Magnesium stearate	5.0

20 The above ingredients are mixed and filled into hard gelatin capsules in 340 mg quantities.

Example 2

25 A tablet Formula is prepared using the ingredients below:

		Quantity
	Ingredient	(mg/tablet)
30	Active Ingredient	25.0
	Cellulose, microcrystalline	200.0
	Colloidal silicon dioxide	10.0
	Stearic acid	5.0

The components are blended and compressed to form tablets, each weighing 240 mg.

Example 3

5 A dry powder inhaler formulation is prepared containing the following components:

	Ingredient	Weight %
10	Active Ingredient	5
	Lactose	95

The active ingredient is mixed with the lactose and the mixture is added to a dry powder inhaling appliance.

Example 4

15 Tablets, each containing 30 mg of active ingredient, are prepared as follows:

	Ingredient	Quantity (mg/tablet)
20	Active Ingredient	30.0 mg
	Starch	45.0 mg
	Microcrystalline cellulose	35.0 mg
	Polyvinylpyrrolidone (as 10% solution in sterile water)	4.0 mg
	Sodium carboxymethyl starch	4.5 mg
25	Magnesium stearate	0.5 mg
	Talc	1.0 mg
	Total	120 mg

30 The active ingredient, starch and cellulose are passed through a No. 20 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders, which are then passed through a 16 mesh U.S. sieve. The granules so produced are dried at 50° to 60°C and passed through a 16 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate, and talc, previously passed through a No. 30 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 120 mg.

Example 5

Capsules, each containing 40 mg of medicament are made as follows:

	Quantity (mg/capsule)
5	Active Ingredient
	40.0 mg
	Starch
	109.0 mg
	Magnesium stearate
	1.0 mg
	Total
	150.0 mg

10 The active ingredient, starch, and magnesium stearate are blended, passed through a No. 20 mesh U.S. sieve, and filled into hard gelatin capsules in 150 mg quantities.

Example 6

15 15 Suppositories, each containing 25 mg of active ingredient are made as follows:

	Ingredient	Amount
20	Active Ingredient	25 mg
	Saturated fatty acid glycerides to	2,000 mg

20 The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of 25 nominal 2.0 g capacity and allowed to cool.

Example 7

Suspensions, each containing 50 mg of medicament per 5.0 mL dose are made as follows:

	Ingredient	Amount
30	Active Ingredient	50.0 mg
	Xanthan gum	4.0 mg
	Sodium carboxymethyl cellulose (11%)	
	Microcrystalline cellulose (89%)	50.0 mg
35	Sucrose	1.75 g
	Sodium benzoate	10.0 mg
	Flavor and Color	q.v.

Purified water to 5.0 mL

The active ingredient, sucrose and xanthan gum are blended, passed through a No. 10 mesh U.S. sieve, and then mixed with a previously made solution of the 5 microcrystalline cellulose and sodium carboxymethyl cellulose in water. The sodium benzoate, flavor, and color are diluted with some of the water and added with stirring. Sufficient water is then added to produce the required volume.

Example 8

10 A formulation may be prepared as follows:

	Ingredient	Quantity (mg/capsule)
15	Active Ingredient	15.0 mg
	Starch	407.0 mg
	Magnesium stearate	3.0 mg
	Total	425.0 mg

20 The active ingredient, starch, and magnesium stearate are blended, passed through a No. 20 mesh U.S. sieve, and filled into hard gelatin capsules in 425.0 mg quantities.

Example 9

25 A formulation may be prepared as follows:

Ingredient	Quantity
Active Ingredient	5.0 mg
Corn Oil	1.0 mL

30 Another preferred formulation employed in the methods of the present invention employs transdermal delivery devices ("patches"). Such transdermal patches may be used to provide continuous or discontinuous infusion of the compounds of the present invention in controlled amounts. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known 35 in the art. *See, e.g.*, U.S. Patent 5,023,252, issued June 11, 1991, herein

incorporated by reference in its entirety. Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

Other suitable formulations for use in the present invention can be found in *Remington's Pharmaceutical Sciences*, edited by E. W. Martin (Mack Publishing Company, 18th ed., 1990).

Biological Examples

Example 1

M₂ Muscarinic Receptor In Vitro Binding Assay

10 The M₂ muscarinic receptor binding activity of compounds of the invention was tested as follows.

SF9 cell membranes containing human M₂ muscarinic receptor was obtained from NEN (Boston, MA). In 96-well microtiter plates, eight serial five-fold dilutions were prepared with the compound to be assayed; the highest concentration 15 was typically 4μM (4x the final concentration). To 100 μl of compound dilution was added 150 μL M₂ receptor membrane preparation in PBS/1.0mM MgCl₂/pH 7.4. 50 μl of 3.2 nM 3H-N-methylscopolamine radioligand was added. The total volume in each well was then 300μl. The filter plate was pre-blocked using 0.3% PEI for at least 15 minutes, and then washed twice with 200 μl PBS. The assay 20 plate was incubated for 1 hour at room temperature with gentle shaking. The contents of the assay plate were then transferred to the filter plate, and washed three times using 200μl PBS. About 40 μl of scint was added to each well and then the plate was allowed to sit at room temperature for 2h, and then counted using a Packard Topcount NXT. Counting was typically performed for 1 minute per well 25 using a standard protocol on a Packard top counter. The raw data was fit to a standard 4-parameter equation given below and a value of IC₅₀ obtained.

$$Y = (a-d)/(1+(x/c)^b) + d \text{ where}$$

Y = cpm

a = total binding

b = slope

c = IC₅₀

x = [compound]

d = nonspecific binding

Representative compounds of the invention were found to have pK_b values of greater than 6, and to have IC_{50} values of less than about 50 μM .

A similar protocol was used to measure M1, M3, M4 and M5 human muscarinic receptor activity.

5

Example 2

Rat Heart Muscarinic Receptor *In Vitro* Binding Assay

Tissue (rat heart) muscarinic receptor binding activity of compounds of the invention was tested as follows.

10 Muscarinic receptor enriched membranes were isolated from whole hearts (Pelfreeze Laboratories). Rat heart tissue was typically prepared as follows. 25 μl of ice cold buffer (20mM HEPES, 100mM NaCl/10mM MgCl₂ at pH 7.5 with "Complete" protease inhibitor cocktail purchased from Boehringer Mannheim was added into an oakridge tube. To the tube was then added 2 g of rat heart (purchased 15 from Harlan). The contents of the tube were then transferred to a wheaton glass cylinder and homogenized using a Polytron homogenizer (setting 22, 15 seconds x2), and then transferred back to the oakridge tube, and centrifuged for 10 minutes at 1500 g. The supernatant was removed and then centrifuged for 20 minutes at 45000 g. The supernatant was removed and the pellet resuspended in 5 mL buffer 20 and transferred to a wheaton glass cylinder. This material was then homogenized using a Potter type glass teflon homogenizer with 7-8 passes. The material was then transferred to an oakridge tube and the total volume was brought up to 25 mL. This material was then centrifuged for 20 minutes at 45000 g, and the pellet re-suspended in 2 mL buffer using 2 passes of a teflon homogenizer, and stored at -80 25 °C until used.

A protocol similar to that used for cloned receptor binding was used: Eight serial five-fold dilutions were prepared with the compound to be assayed; the highest concentration was typically 4 μM (4x the final concentration). To 50 μl of compound dilution in a 96-well assay plate was added an appropriate amount of rat 30 heart membrane (usually 12.5 μl of membrane prep in 87.5 μl of 20mM HEPES, 100mM NaCl/10mM MgCl₂ at pH 7.5). The amount of membrane added depends

in general on the results of signal optimization, and ranges from 6.25-12.5 μ l. Last, 50 μ l of 2.12 nM 3H-N-methylscopolamine radioligand was added. The total volume in each well was 200 μ l. The filter plate was pre-blocked using 0.3% PEI for at least 15 min., and then washed twice with 200 μ l PBS. The assay plate was 5 incubated for 1 h at room temperature with gentle shaking. The contents of the assay plate were then transferred to the filter plate, and washed three times using 200 μ l PBS. About 40 μ l of scint was added to each well and then the plate was allowed to sit at room temperature for 18 h, and then counted using a Packard Topcount NXT. Counting was typically performed for 1 min., per well using a 10 standard protocol on the Packard counter. The data was fit to normal isotherms and values for inhibition constants were extracted. Representative compounds of the invention were found to have pK_b values of greater than 6, and to have IC_{50} values of less than about 50 μ m.

A similar procedure was used to measure muscarinic receptor binding at rat 15 submaxillary gland, rat bladder, rat submandibular gland, guinea pig heart, guinea pig submaxillary gland, guinea pig bladder, and guinea pig submandibular gland, as well as in similar human tissues..

Example 3

20 Rat Bladder M₃ *In Vitro* Binding Assay

Bladder was comprised of both M₂ and M₃ muscarinic receptors. The ratio was typically 4:1 M₂:M₃. In order to measure binding of test compounds to one of M₂ or M₃, the other was blocked with a reversible ligand that binds selectively to that receptor. The following example illustrates the procedure for M₃ bladder 25 binding.

Membranes from rat bladder were prepared in a similar fashion to that used to isolate heart membrane above. Eight serial five-fold dilutions were prepared with the compound to be assayed in compound dilution buffer (20 mM HEPES/100mM NaCl/10mM MgCl₂/4 μ M Methocramine); the highest 30 concentration was typically 4 μ M (4x the final concentration). The concentration of methocramine was sufficient to block >99% of the M2 receptor in bladder, but

less than 40% of the M_3 receptor in bladder. To 50 μ l of compound dilution in a 96-well assay plate was added an appropriate amount of rat heart membrane (usually 25 μ l of membrane prep in 75 μ l of 20 mM HEPES, 100 mM NaCl/10 mM MgCl₂ at pH 7.5). The amount of membrane added depended in general on the 5 results of signal optimization, and ranged from 12.5-25. Last, 50 μ l of 2.12 nM ³H-N-methylscopolamine radioligand in compound dilution buffer was added. The total volume in each well was 200 μ l. The final concentration of methoctramine was 2 μ M. The filter plate was pre-blocked using 0.3% PEI for at least 15 mins., and then washed twice with 200 μ l PBS. The assay plate was 10 incubated for 1 hour at room temperature with gentle shaking. The contents of the assay plate was then transferred to the filter plate, and washed three times using 200 μ l PBS. About 40 μ l of scint was added to each well, the plate was allowed to sit at room temperature for 18h, and then counted using a Packard Topcount NXT. Counting was typically performed for 1 minute per well using a standard protocol on 15 the Packard counter. The data was fit to normal isotherms and values for inhibition constants were extracted. Representative compounds of the invention were found to have IC₅₀ values of less than about 500 μ m.

A similar procedure was used to measure binding at bladder M_2 , but in this case, 2 μ M Darifenacin was used to block >99% of the M_2 receptor, but minimal 20 M_3 receptor.

Example 4

Ex Vivo Rat Bladder Contraction Assay

The ability of the test compound to inhibit cholinergically stimulated bladder contraction was tested as follows.

25 Male Sprague-Dawley rats weighing 250 – 300 g are killed by CO₂ overdose. The bladder was removed and placed in a petri dish containing Krebs-Henseleit solution at room temperature. The apex and dome areas of the bladder were discarded and the remaining tissue cut into longitudinal strips (4 from each rat). The strips were mounted in an organ bath containing Krebs-Henseleit solution at 37 30 °C, under a resting tension of 0.5 g. The tissues were allowed to equilibrate for 60 min., (washes at 0, 30 and 60 min.). Tension was readjusted to 1 g as necessary. A

cumulative concentration response curve to carbachol (10-8 M to 10-5 M (e.g.) in 3-fold increments) was constructed in each tissue. Tissues were then washed every 5 min., for 30 min., and tension readjusted to 1 g. After additional 30 min., muscarinic antagonist (typically 1x10-7 M) or vehicle was added. Thirty minutes

5 after antagonist or vehicle addition, a cumulative concentration response curve to carbachol (10-8M to 10-3M (e.g.)) was constructed. Data from each concentration response curve was expressed as a percentage of the maximum contraction to carbachol. The EC₅₀ values were calculated. The concentration-ratios were calculated taking into account any spontaneous shift in the control tissue. For

10 competitive antagonists, the pK_b value was calculated using the following equation:

$$pK_b = -\log [\text{antagonist concentration}]$$

CR-1

15 Representative compounds of the invention were found to have pK_b values of greater than 5.

Example 5

In Vivo Rat Salivation Assay

20 Male Sprague-Dawley rats weighing 250 – 300 g were anesthetized with pentobarbital (60 mg/kg i.p.). Rats were placed on a heated blanket under a 20 degree incline. A swab was placed in the rat's mouth. Muscarinic antagonist or vehicle was administered i.v. via the tail vein. After 5 min., oxotremorine (0.3 mg/kg) was administered s.c.. The swab was discarded and replaced by a pre-
25 weighed swab. Saliva was then collected for 15 min. After 15 min., the swab was weighed and the difference in its weight was used to calculate the antisecretory potency of the antagonists. The data was fit to normal isotherms and ID₅₀ values were extracted.

30

Example 6

In Vivo Bladder Assay

Male Sprague-Dawley rats weighing 250 – 300 g were anesthetized with urethane (1.3 g/kg, i.p.), inactin (25 mg/kg, i.p.), and xylazine (4 mg, i.p.). The jugular (or femoral) vein was isolated and ligated and a small incision was made in the vein distal to the ligation. A catheter (micro-Renathane tubing (0.014 mm ID x 5 0.033 mm OD) filled with saline was inserted into the vein and secured into place with suture thread. The trachea was isolated and placed in a small hole between two of the rings. Tubing (1.57 mm ID x 2.08 mm OD) was inserted into the trachea and tied into place with suture thread. The incision was closed leaving the tubing exposed. The tracheotomy was to prevent the animal from asphyxiating on his own 10 saliva following oxotremorine administration. The stomach was shaved and then cleaned with ethanol. A midline sagital incision was made in the skin and muscle layers of the lower stomach. The bladder was exposed and the saline filled cannula (22-gauge needle attached to a pressure transducer with PE 90 tubing) was inserted into the apex of the bladder to the most distal part of the bladder. The bladder was 15 placed back into the peritoneal cavity. The bladder was emptied manually by disconnecting the cannula and allowing the contents to flow out until the bladder was approximately 1 cm in diameter. The incision was closed with suture thread, first the muscle layer, then the skin in order to keep the bladder moist and warm. The exposed portion of the cannula to the skin surface was sutured to hold it in 20 place. After 15 min. oxotremorine (0.3 mg/kg, SC, baseweight) was injected. After 10 min., (or until baseline stabilized) a test compound or a reference standard was injected with a dose equivalent to 0.005 – 0.01 mg/kg, IV, baseweight of atropine that produced a 30-70% decrease in intraluminal pressure. After 5 min., a high dose of atropine 0.1 mg/kg was injected, i.v., to establish the true 100% 25 inhibition point.

For data analysis, the oxotremorine response (zero inhibition) was determined by measuring the mean pressure 1 minute prior to the antagonist injection. Then, to assess antagonist inhibition, mean pressure was mesured beginning at 1 minute and ending 2 minutes after antagonist administration. If the 30 pressure had not leveled off after 1 minute, a wait was initiated until it was stable and then a 1-minute sample of the mean was taken. Lastly, to determine the true

100% inhibition point, the mean pressure was measured beginning 1 minutes and ending 2 minutes after the high dose atropine challenge. The percent inhibition by the antagonist can be determined by the ratio of the decrease from the zero to 100% values.

5 The formula is: oxotremorine mean – treatment mean *100
oxotremorine mean – atropine mean.

Additionally, the activity of a compound of the invention on other tissues can be determined using screening protocols that are known in the art. For example, an 10 assessment of increased locomotor activity (assay for CNS penetration) can be carried out as described by Sipos ML, et al., (1999) *Psychopharmacology* 147(3):250-256; an assessment of the effects of a compound on gastrointestinal motility can be carried out as described by Macht DI, and Barba-Gose J (1931) *J Am Pharm Assoc* 20:558-564; an assessment of the effects of a compound on pupil 15 diameter (mydriasis) can be carried out as described by Parry M, Heathcote BV (1982) *Life Sci* 31:1465-1471; and an assessment of a compounds effects on urinary bladder in dog can be carried out as described by Newgreen DT, et al. (1996) *J Urol* 155:600A.

Preferred compounds of the invention may display selectivity for one or 20 more tissues over other tissues. For example, compounds of the invention that are useful for treating urinary incontinence may show higher activity in the assay of Example 6 than in the assay of Example 5.

Preferred compounds useful for treating urinary incontinence and irritable bowel syndrome have greater antagonist activity at the M₂ receptor than at the M₃ 25 receptor or the other muscarinic receptors.

Preferred compounds useful for treating unwanted salivation have greater antagonist activity at the M₃ receptor than at the M₂ receptor or the other muscarinic receptors.

The foregoing invention has been described in some detail by way of 30 illustration and example, for purposes of clarity and understanding. It will be obvious to one of skill in the art that changes and modifications may be practiced

within the scope of the appended claims. Therefore, it is to be understood that the above description is intended to be illustrative and not restrictive. The scope of the invention should, therefore, be determined not with reference to the above description, but should instead be determined with reference to the following

5 appended claims, along with the full scope of equivalents to which such claims are entitled.

All patents, patent applications and publications cited in this application are hereby incorporated by reference in their entirety for all purposes to the same extent as if each individual patent, patent application or publication were so individually denoted.